3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of synthetic vitreous fibers. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for synthetic vitreous fibers. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No studies were located in which acute- or intermediate-duration inhalation exposure to synthetic vitreous fibers caused mortality in humans. As discussed in Sections 3.2.1.2 and 3.2.1.7, cohort mortality studies of workers involved in the manufacture of fiberglass, rock wool, slag wool, and refractory ceramic fibers have not found consistently increased risk of mortality associated with nonmalignant or malignant respiratory disease.

None of the animal studies described below observed increased risk of death after inhalation exposure to synthetic vitreous fibers.

3.2.1.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, endocrine, dermal, ocular, or body weight effects in humans or animals after inhalation exposure to synthetic vitreous fibers. The principal target organ of inhaled synthetic vitreous fibers is the respiratory system.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects from inhalation exposure to synthetic vitreous fibers are summarized in Table 3-1 and plotted in Figure 3-1.

Although there are epidemiological studies of workers involved in the manufacture of synthetic vitreous fibers such as refractory ceramic fibers, the results do not characterize exposure-response relationships for potential health effects in humans. In contrast, animal inhalation studies identify several types of respiratory effects from various types of synthetic vitreous fibers and provide information on exposure-response relationships. Thus, data in Table 3-1 and Figure 3-1 are restricted to reliable NOAEL and LOAEL values from animal inhalation toxicity studies. Units of exposure in animal studies include gravimetric measurements (mg/m^3), which include the weight of nonfibrous particles present in air samples, and fiber count measurements (# fibers/cc), which rely on microscopically aided counting of fiber numbers in air samples. The most frequently reported unit of exposure among the available animal toxicity studies is based on the WHO fiber counting rules (i.e., a fiber is counted as a particle with length

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
	ACUTE EXPOSURE						
	Systemic						
1	Rat (Fischer- 344)	5 d 6 hr/d (nose only)	Resp		1700[b] M (pulmonary and pleural inflammation; increased lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1994 RCF1
2	Rat (Fischer- 344)	5 d 6 hr/d	Resp		2645 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1996a, 1996c RCF1
3	Hamster (Golden Syrian)	5 d 6 hr/d (nose only)	Resp		1700[b] M (pulmonary and pleural inflammation; increased lung mesothelial cell proliferation)		Everitt et al. 1994 RCF1
	INTERMEDIATE EXPOSURE						
	Systemic						
4	Rat (Wistar)	3 wk 6 hr/day 5 d/wk (nose only)	Resp			679 F (very slight interstitial fibrosis, pulmonary inflammation, reduced alveolar clearance)	Bellman et al. 2001 RCF1
5	Rat (Wistar)	3 wk 6 hr/day 5 d/wk (nose only)	Resp			481 F (very slight interstitial fibrosis, pulmonary inflammation)	Bellman et al. 2001 RCF1a

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
6	Rat (Wistar)	1 yr 7 hr/d 5 d/wk	Resp		1119 M (pulmonary inflammation)		Cullen et al. 2000 100/475 special purpose glass fiber
7	Rat (Wistar)	1 yr 7 hr/d 5 d/wk	Resp			1022 M (advanced pulmonary fibrosis; pulmonary inflammation)	Cullen et al. 2000 104 E-glass special purpose glass fiber
8	Rat (Fischer- 344)	4 wk 4 hr/d 5 d/wk (nose only)	Resp		300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1
9	Rat (Fischer- 344)	12 wk 4 hr/d 5 d/wk (nose only)	Resp		300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1
10	Rat (Fischer- 344)	12 wk 4 hr/d 5d/wk	Resp		296 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1999 RCF1

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
11	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		29 M (minimal pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
			Bd Wt	232 M			
12	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		29 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
			Bd Wt	232 M			
13	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		29 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
			Bd Wt	232 M			
14	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		41 M (minimal pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool
			Bd Wt	246 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
15	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		41 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool
			Bd Wt	256 M			
16	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		41 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool
			Bd Wt	246 M			
17	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		180 M (pulmonary inflammation)		Hesterberg et al. 1998b X607
			Hepatic	180 M			
			Renal	180 M			
			Bd Wt	180 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
18	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		180 M (pulmonary inflammation)		Hesterberg et al. 1998b X607
			Hepatic	180 M			
			Renal	180 M			
			Bd Wt	180 M			
19	Rat (Fischer- 344)	1 yr 6 hr/d 5 d/wk (nose only)	Resp		180 M (pulmonary inflammation)		Hesterberg et al. 1998b X607
			Hepatic	180 M			
			Renal	180 M			
			Bd Wt	180 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
20	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		291 M (minimal pulmonary inflammation)		Kamstrup et al. 2001 MMVF34 rock wool
			Bd Wt	291 M			
21	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		291 M (minimal-to-slight pulmonary inflammation; bronchoalveolar collagen deposition without fibrosis)		Kamstrup et al. 2001 MMVF34 rock wool
			Bd Wt	291 M			
22	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		291 M (minimal-to-slight pulmonary inflammation)		Kamstrup et al. 2001 MMVF34 rock wool
			Bd Wt	291 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
23	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		220 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			
24	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		220 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
25	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk (nose only)	Resp			220 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			
26	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp			220 M (mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
27	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		182 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			
28	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp			182 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
29	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk (nose only)	Resp			182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			
30	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp			182 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
31	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		153 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			
32	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		153 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
33	Rat (Fischer- 344)	9 mo 6 hr/d 5 d/wk (nose only)	Resp		153 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			
34	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp			153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
35	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		26 M (minimal-to-mild pulmonary inflammation)		Mast et al. 1995a, 1995b RCF1
			Cardio	187 M			
			Hepatic	187 M			
			Renal	187 M			
			Bd Wt	187 M			
36	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		26 M (minimal-to-mild pulmonary inflammation)	187 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a, 1995b RCF1
			Cardio	187 M			
			Hepatic	187 M			
			Renal	187 M			
			Bd Wt	187 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
37	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		36 M (minimal-to-mild pulmonary inflammation)	91 M (minimal-to-mild interstitial fibrosis)	Mast et al. 1995a, 1995b RCF1
			Cardio	234 M			
			Hepatic	234 M			
			Renal	234 M			
			Bd Wt	234 M			
38	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		34 M (pulmonary inflammation)		McConnell et al. 1994 MMVF21 rock wool
			Cardio	243 M			
			Hepatic	243 M			
			Renal	243 M			
			Bd Wt	243 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
39	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		34 M (pulmonary inflammation)		McConnell et al. 1994 MMVF21 rock wool
			Cardio	243 M			
			Hepatic	243 M			
			Renal	243 M			
			Bd Wt	243 M			
40	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		34 M (pulmonary inflammation)		McConnell et al. 1994 MMVF21 rock wool
			Cardio	243 M			
			Hepatic	243 M			
			Renal	243 M			
			Bd Wt	243 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
41	Rat (Fischer- 344)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		30 M (pulmonary inflammation)		McConnell et al. 1994 MMVF22 slag wool
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			
42	Rat (Fischer- 344)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		30 M (pulmonary inflammation)		McConnell et al. 1994 MMVF22 slag wool
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
43	Rat (Fischer- 344)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		30 M (pulmonary inflammation)		McConnell et al. 1994 MMVF22 slag wool
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			
44	Rat (Wistar)	12 mo 5 hr/d 4 d/wk (nose only)	Resp	252			Muhle et al. 1987 100/475 special purpose glass fiber
45	Hamster (Golden Syrian)	4 wk 4 hr/d 5 d/wk (nose only)	Resp		300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation)		Everitt et al. 1997 RCF1

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
46	Hamster (Golden Syrian)	12 wk 4 hr/d 5 d/wk (nose only)	Resp			300 M (pulmonary and pleural inflammation; incr. lung and diaphragm mesothelial cell proliferation; early signs of pleural fibrosis)	Everitt et al. 1997 RCF1
47	Hamster (Golden Syrian)	12 wk 4 hr/d 5d/wk	Resp		296 M (pulmonary and pleural inflammation)		Gelzleichter et al. 1999 RCF1
48	Hamster (Golden Syrian)	7 wk 6 hr/d 5 d/wk (nose only)	Resp		316 M (pulmonary inflammation)		Hesterberg et al. 1999 MMVF10 glass wool
49	Hamster (Golden Syrian)	13 wk 6 hr/d 5 d/wk (nose only)	Resp		36 M (pulmonary inflammation)		Hesterberg et al. 1999 MMVF10 glass wool

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
50	Hamster (Golden Syrian)	3 mo 5 d/wk 6 hr/d (nose only)	Resp		215 M (mild-to-moderate pulmonary inflammation)		McConnell et al. 1995 RCF1
			Cardio	215 M			
			Hepatic	215 M			
			Renal	215 M			
			Bd Wt	215 M			
51	Hamster (Golden Syrian)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		339 M (minimal-to-moderate pulmonary inflammation)		McConnell et al. 1999 MMVF10a glass wool
			Bd Wt	339 M			
52	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk (nose only)	Resp		339 M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999 MMVF10a glass wool
			Bd Wt	339 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
53	Hamster (Golden Syrian)	12 mo 6 hr/d 5 d/wk (nose only)	Resp		339 M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999 MMVF10a glass wool
			Bd Wt	339 M			
54	Hamster (Golden Syrian)	3 mo 6 hr/d 5 d/wk (nose only)	Resp		310 M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999 MMVF33 special purpose glass
			Bd Wt	310 M			
55	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk (nose only)	Resp			310 M (minimal to mild pulmonary and pleural fibrosis, pulmonary inflammation)	McConnell et al. 1999 MMVF33 special purpose glass
			Bd Wt	310 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
56	Hamster (Golden Syrian)	6 mo 6 hr/d 5 d/wk (nose only)	Resp			310 M (mild pulmonary and pleural fibrosis, pulmonary inflammation)	McConnell et al. 1999 MMVF33 special purpose glass
			Bd Wt	310 M			
57	Baboon	8 mo 7 hr/d 5 d/wk (nose only)	Resp		1122[b] M (pulmonary inflammation, scant ferruginous bodies)		Goldstein et al. 1983 C102-C104 blend glass wool
	Cancer						
58	Rat (Wistar)	1 yr 7 hr/d 5 d/wk				1022 M (CEL: pleural mesotheliomas, lung adenomas and carcinomas)	Cullen et al. 2000 104 E-glass special purpose glass fiber
59	Hamster (Golden Syrian)	40 wk 5 d/wk 6 h/d (nose only)				215 M (CEL: pleural mesotheliomas)	McConnell et al. 1995 RCF1

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Systemic						
60	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		29 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
			Bd Wt	232 M			
61	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp		29 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF10 glass wool
			Bd Wt	232 M			
62	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		41 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool
			Bd Wt	246 M			
63	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp		41 M (minimal-to-mild pulmonary inflammation)		Hesterberg et al. 1993 MMVF11 glass wool
			Bd Wt	246 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
64	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		180 M (pulmonary inflammation)		Hesterberg et al. 1998b X607
			Hepatic	180 M			
			Renal	180 M			
			Bd Wt	180 M			
65	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp		180 M (pulmonary inflammation)		Hesterberg et al. 1998b X607
			Hepatic	180 M			
			Renal	180 M			
			Bd Wt	180 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
66	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		291 M (minimal-to-slight pulmonary inflammation)		Kamstrup et al. 2001 MMVF34 rock wool
			Bd Wt	291 M			
67	Rat (Fischer- 344)	24 mo 6 hr/d 5 d/wk (nose only)	Resp		291 M (minimal-to-moderate pulmonary inflammation)		Kamstrup et al. 2001 MMVF34 rock wool
			Bd Wt	291 M			
68	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk (nose only)	Resp			220 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
69	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp			220 M (mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			
70	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp			220 M (mild-to-moderate interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF2
			Cardio	220 M			
			Hepatic	220 M			
			Renal	220 M			
			Bd Wt	220 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
71	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk (nose only)	Resp			182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			
72	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp			182 M (mild interstitial fibrosis, minimal-to-mild pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
73	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp			182 M (mild-to-moderate interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF3
			Cardio	182 M			
			Hepatic	182 M			
			Renal	182 M			
			Bd Wt	182 M			
74	Rat (Fischer- 344)	15 mo 6 hr/d 5 d/wk (nose only)	Resp			153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
75	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp			153 M (minimal-to-mild interstitial fibrosis, minimal pleural fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			
76	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp			153 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a RCF4
			Cardio	153 M			
			Hepatic	153 M			
			Renal	153 M			
			Bd Wt	153 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
77	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		26 M (minimal-to-mild pulmonary inflammation)	75 M (minimal-to-mild interstitial fibrosis)	Mast et al. 1995a, 1995b RCF1
			Cardio	187 M			
			Hepatic	187 M			
			Renal	187 M			
			Bd Wt	187 M			
78	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp		26[c] M (minimal-to-mild pulmonary inflammation)	75 M (minimal-to-mild interstitial fibrosis, pulmonary inflammation)	Mast et al. 1995a, 1995b RCF1
			Cardio	187 M			
			Hepatic	187 M			
			Renal	187 M			
			Bd Wt	187 M			

[a]

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
79	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		34 M (pulmonary inflammation)	150 M (mild pulmonary fibrosis, pulmonary inflammation)	McConnell et al. 1994 MMVF21 rock wool
			Cardio	243 M			
			Hepatic	243 M			
			Renal	243 M			
			Bd Wt	243 M			
80	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)	Resp		34 M (pulmonary inflammation)	150 M (mild pulmonary fibrosis, pulmonary inflammation)	McConnell et al. 1994 MMVF21 rock wool
			Cardio	243 M			
			Hepatic	243 M			
			Renal	243 M			
			Bd Wt	243 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
81	Rat (Fischer- 344)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		30 M (pulmonary inflammation)		McConnell et al. 1994 MMVF22 slag wool
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			
82	Rat (Fischer- 344)	24 mo 6 hr/d 5 d/wk (nose only)	Resp		30 M (pulmonary inflammation)		McConnell et al. 1994 MMVF22 slag wool
			Cardio	213 M			
			Hepatic	213 M			
			Renal	213 M			
			Bd Wt	213 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
83	Hamster (Golden Syrian)	18 mo 5 d/wk 6 hr/d (nose only)	Resp			215 M (mild-to-moderate interstitial fibrosis, moderate-to-marked pleural fibrosis, pulmonary inflammation, mesothelial hyperplaisa)	McConnell et al. 1995 RCF1
			Cardio	215 M			
			Hepatic	215 M			
			Renal	215 M			
			Bd Wt	215 M			
84	Hamster (Golden Syrian)	18 mo 6 hr/d 5 d/wk (nose only)	Resp		339 M (minimal-to-mild pulmonary inflammation)		McConnell et al. 1999 MMVF10a glass wool
			Bd Wt	339 M			

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
85	Hamster (Golden Syrian)	18 mo 6 hr/d 5 d/wk (nose only)	Resp			310 M (mild pleural and interstitial fibrosis; mesothelial hyperplasia)	McConnell et al. 1999 MMVF33 special purpose glass
			Bd Wt	310 M			
86	Baboon	18 mo 7 hr/d 5 d/wk (nose only)	Resp			1122[b] M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies)	Goldstein et al. 1983 C102-C104 blend glass wool
87	Baboon	30 mo 7 hr/d 5 d/wk (nose only)	Resp			1122[b] M (focal peribronchiolar fibrosis; numerous pulmonary ferruginous bodies)	Goldstein et al. 1983 C102-C104 blend glass wool
	Cancer						
88	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)				182 M (CEL: pulmonary adenomas and carcinomas, pleural mesotheliomas)	Mast et al. 1995a RCF3
89	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)				153 M (CEL: pleural mesothelioma)	Mast et al. 1995a RCF4

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
90	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)				220 M (CEL: pulmonary carcinomas, pleural mesotheliomas)	Mast et al. 1995a RCF2
91	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)				187 M (CEL: pulmonary adenomas and carcinomas)	Mast et al. 1995a, 1995b RCF1
92	Rat (Fischer- 344)	2 yr 6 hr/d 5 d/wk (nose only)				75 M (CEL: pleural mesothelioma)	Mast et al. 1995a, 1995b RCF1
93	Hamster (Golden Syrian)	18 mo 5 d/wk 6 hr/d (nose only)				215 M (CEL: pleural mesotheliomas)	McConnell et al. 1995 RCF1
94	Hamster (Golden Syrian)	78 wk 6 hr/d 5 d/wk (nose only)				310 M (CEL: pleural mesothelioma)	McConnell et al. 1999 MMVF33 special purpose glass

Table 3-1 Levels of Significant Exposure to Synthetic Vitreous Fibers - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (WHO fibers/cc)	LOAEL Less Serious (WHO fibers/cc)	LOAEL Serious (WHO fibers/cc)	Reference Chemical Form
95	Hamster (Golden Syrian)	24 mo 6 hr/d 5 d/wk (nose only)				200 (CEL: pleural mesothelioma)	Smith et al. 1987 RCF

a The number corresponds to entries in Figure 3-1.
Doses are reported as WHO fibers/cc; (WHO fibers = particles with length >5µm, diameter <3 µm, and a length:width ratio =3:1)

b Dose reported as NIOSH fibers/cc; (NIOSH fibers = particles with length >5µm and a length:width ratio =3:1)

c Used to derive a chronic inhalation minimal risk level (MRL) of 0.03 WHO fibers/cc for refractory ceramic fibers, as described in detail in Appendix A. The MRL was derived using a benchmark dose modeling approach and a cross-species dosimetric scaling factor derived from lung deposition and clearance models for RCF1 fibers in rats and humans. Continuous-variable models in the EPA Benchmark Dose Software were fit to data for macrophage aggregation, bronchiolization, collagen deposition at the bronchoalveolar junction, and lung weight in F344 male rats exposed to RCF1 for 2 years. The best-fitting model for each endpoint was used to calculate benchmark concentrations and their lower 95% confidence limits (BMCs and BMCLs in units of total fibers/cc) associated with 10% increase in lung weight, compared with controls, or a mean minimal score of 1.0 (on a 0-5 scale) for the lesions. The point of departure for the MRL was selected as the BMCL associated with the most sensitive endpoint, the BMCL for macrophage aggregation - 9 total fibers/cc. The selected rat BMCL was converted to a human equivalent concentration (BMCLHEC =1 WHO fibers/cc) using a cross-species scaling factor of 0.07. The BMCLHEC for macrophage aggregation was divided by an uncertainty factor of 30 (3 for interspecies extrapolation with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = Female; G = gavage; Gastro = gastrointestinal; gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); MMVF = man-made vitreous fiber; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; NS = not specified; RCF = refractory ceramic fiber; Resp = respiratory; (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation

Acute (≤14 days)

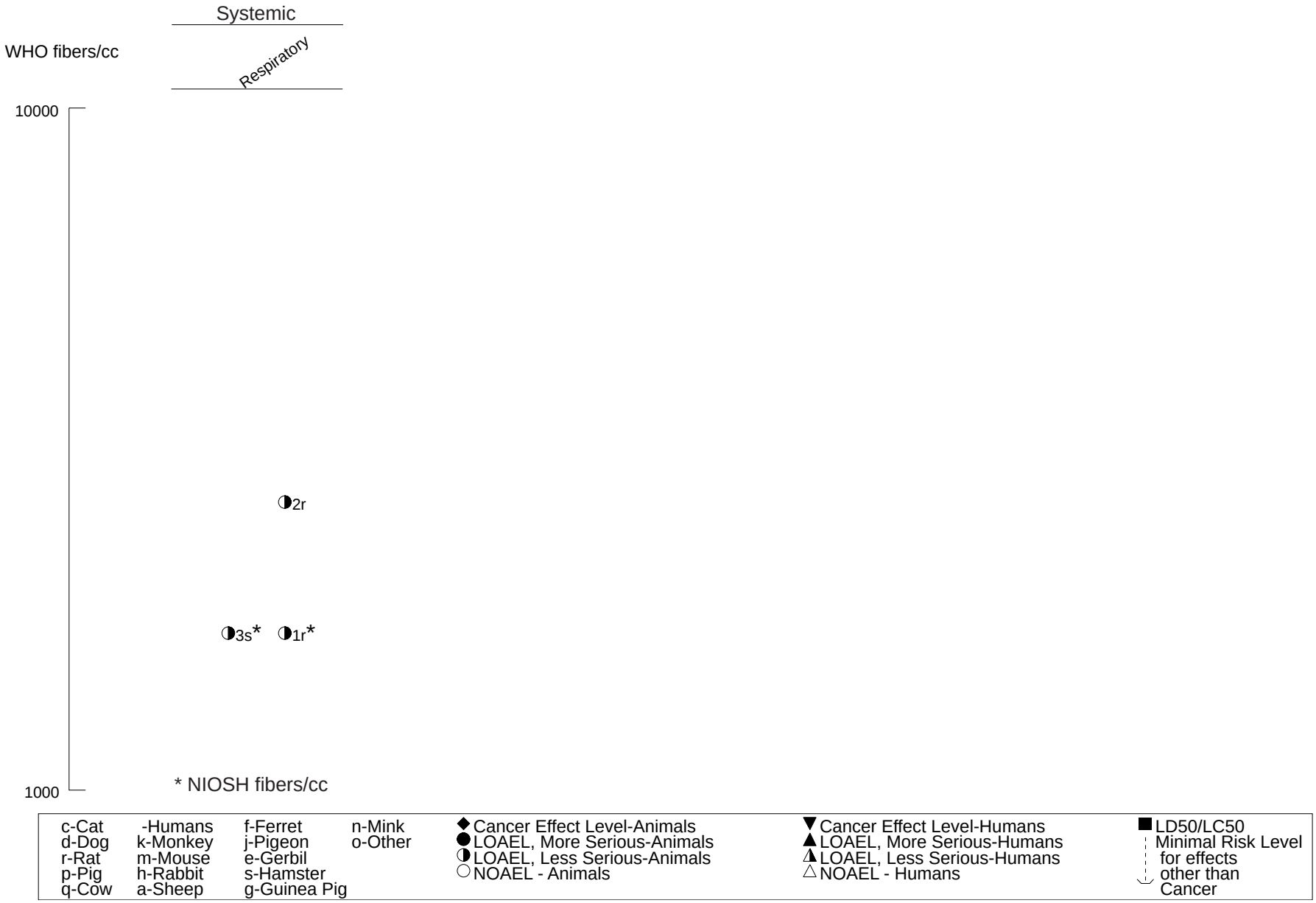


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

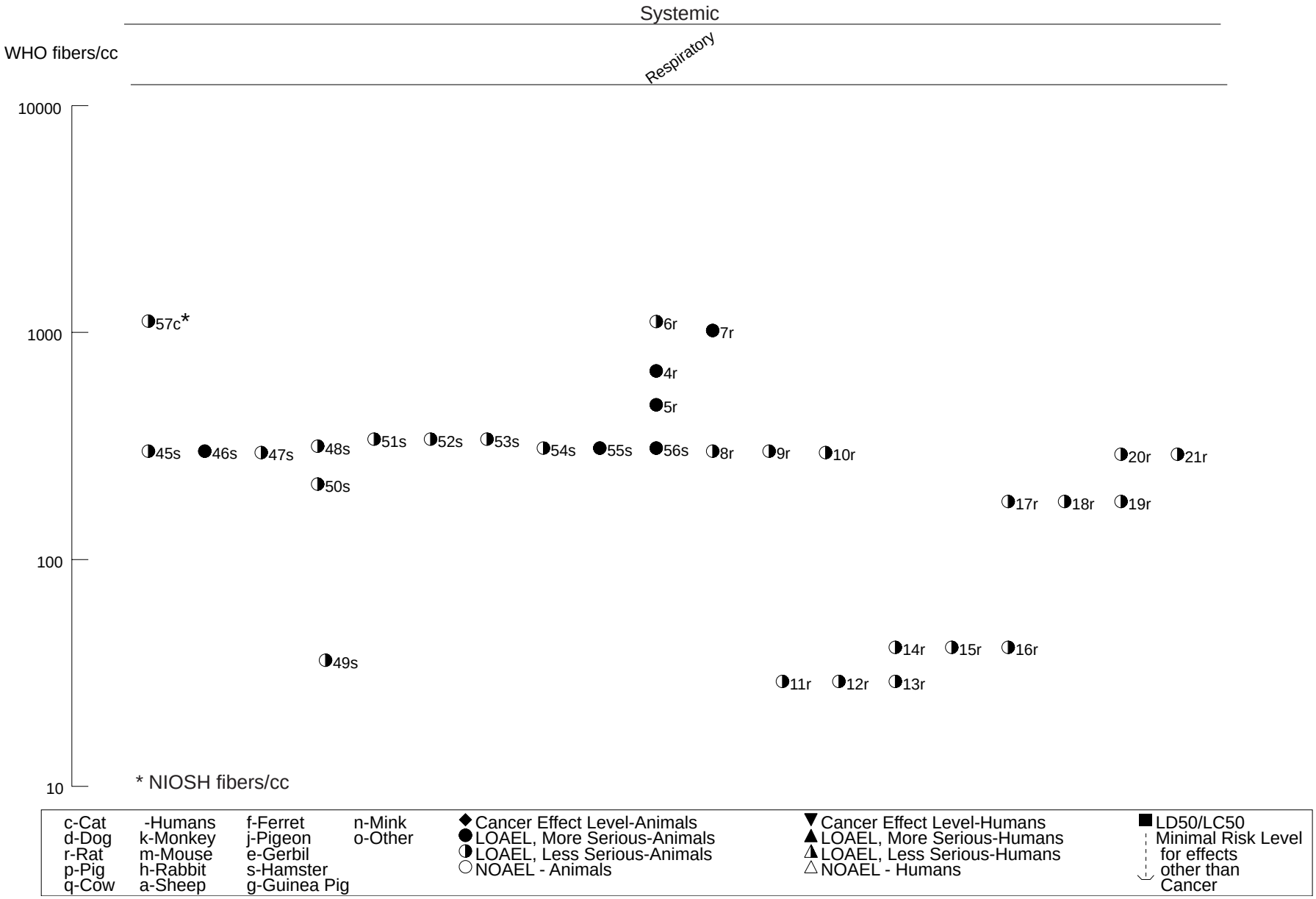


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

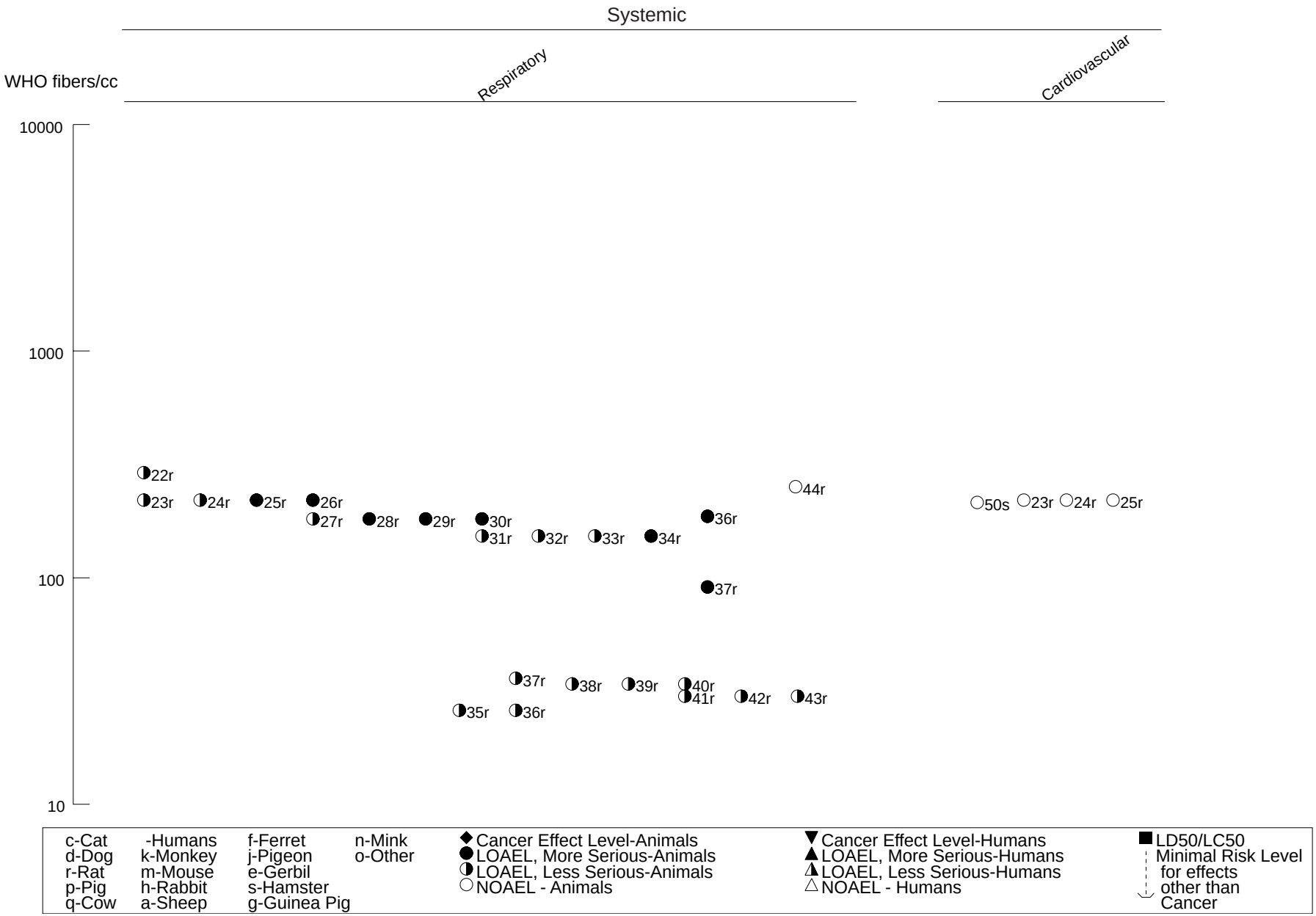


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

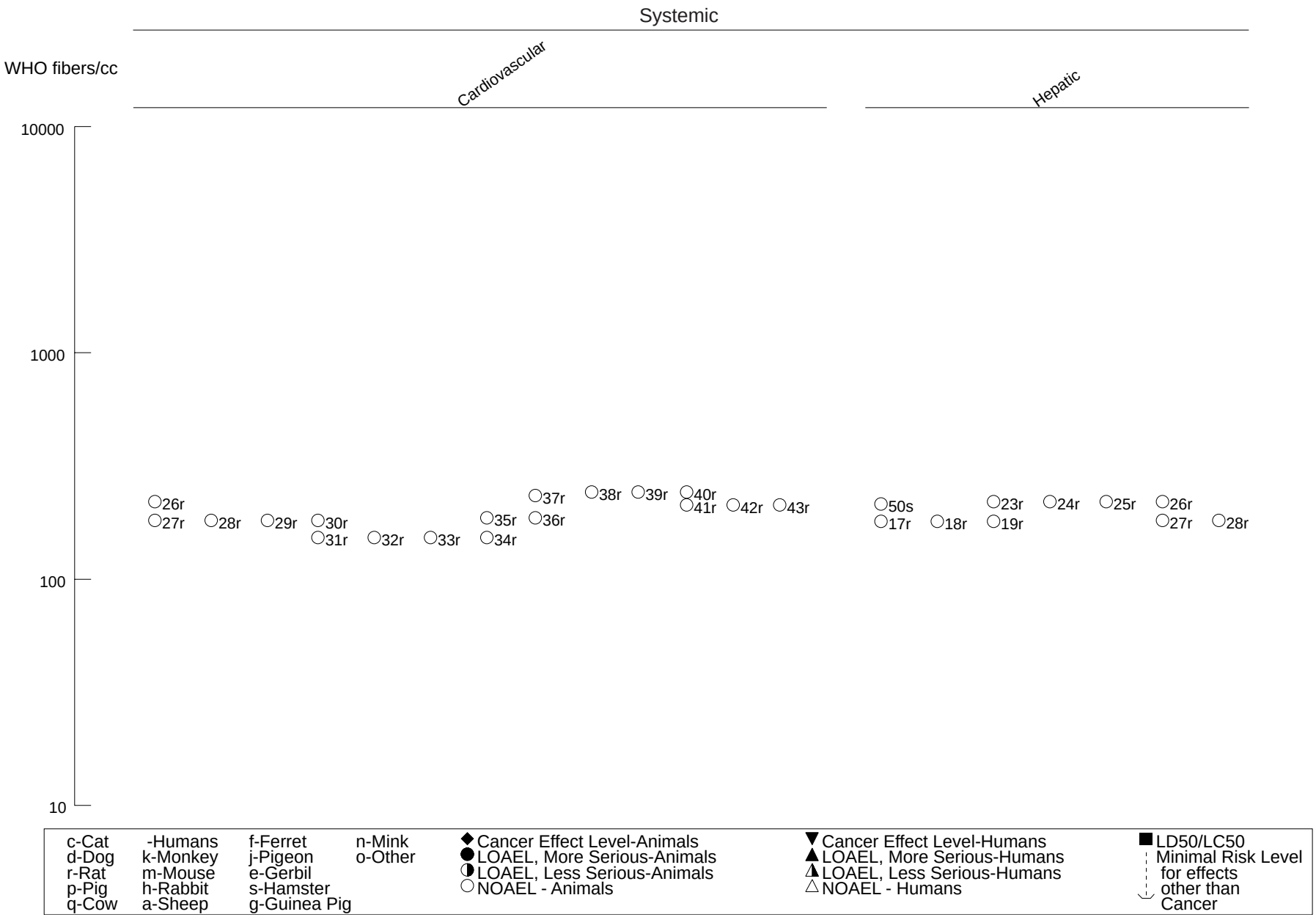


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

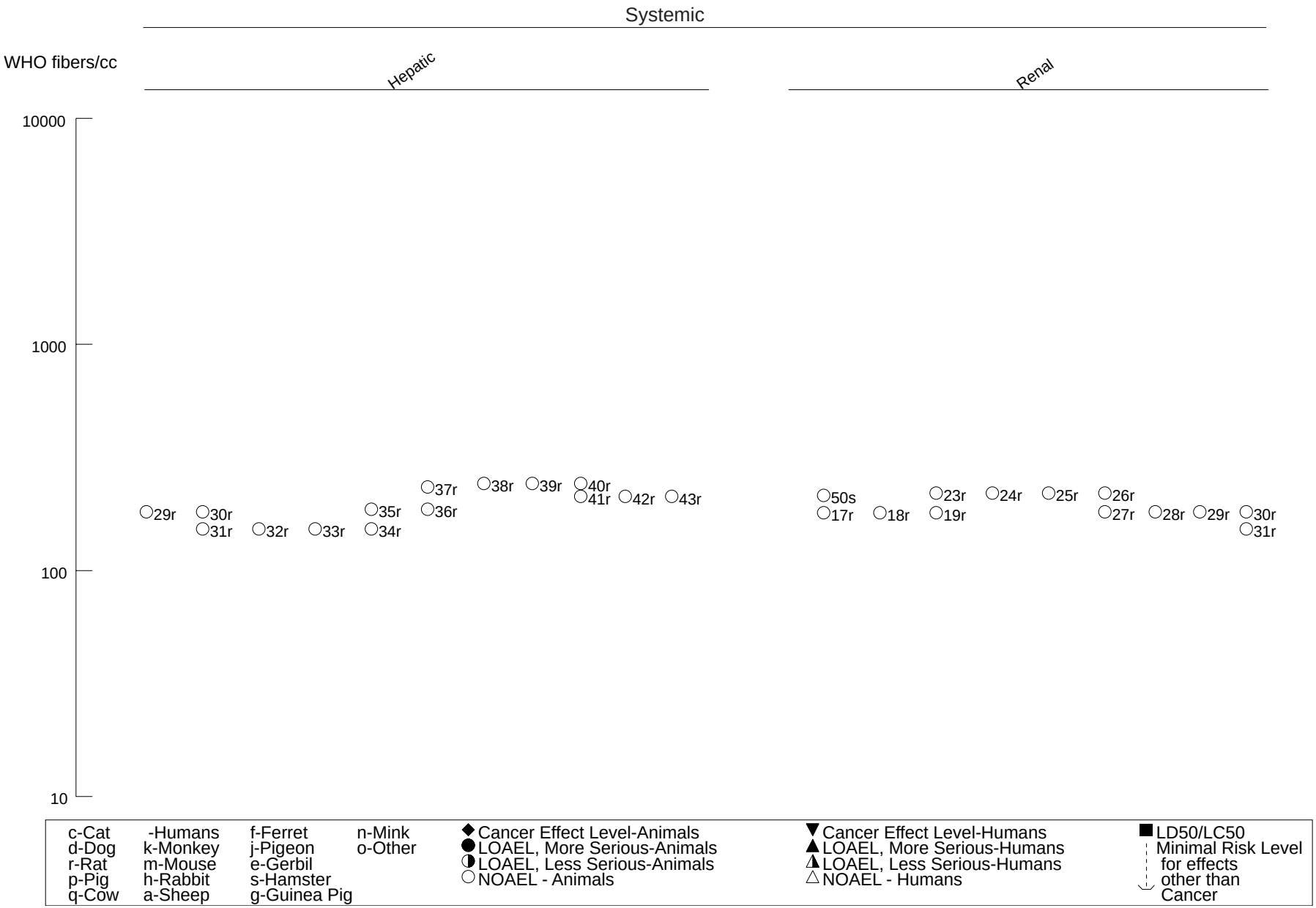


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

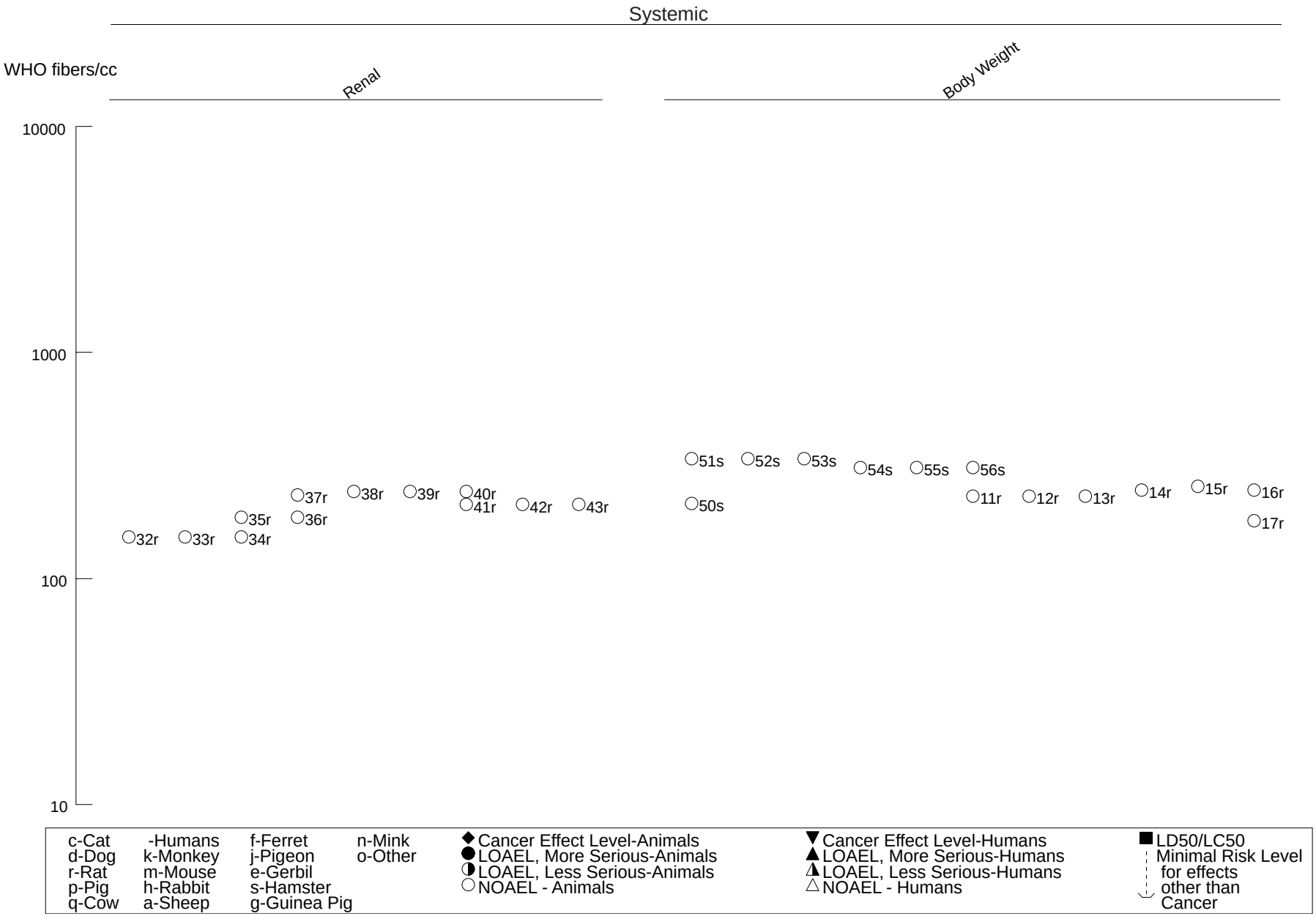


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Intermediate (15-364 days)

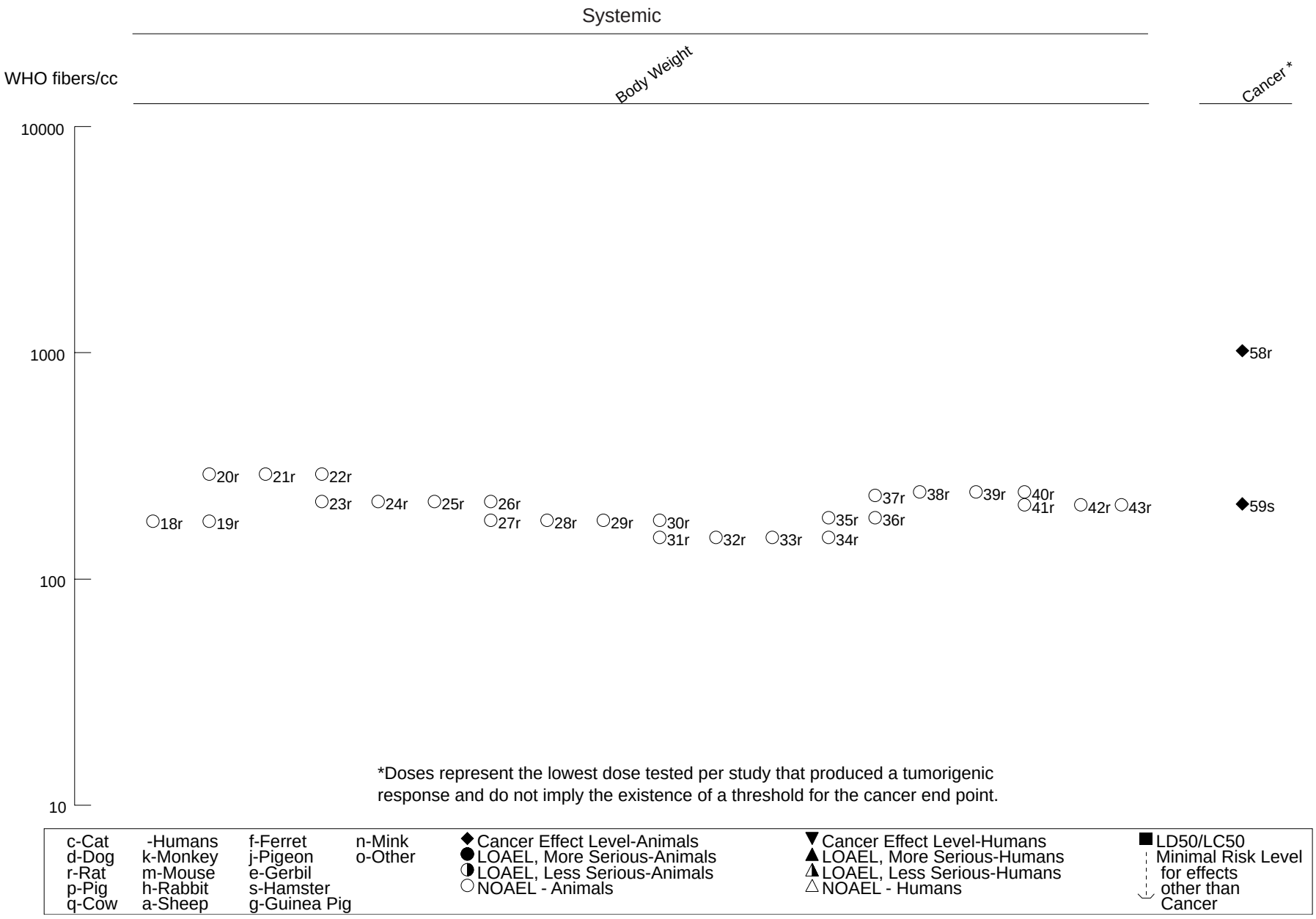


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

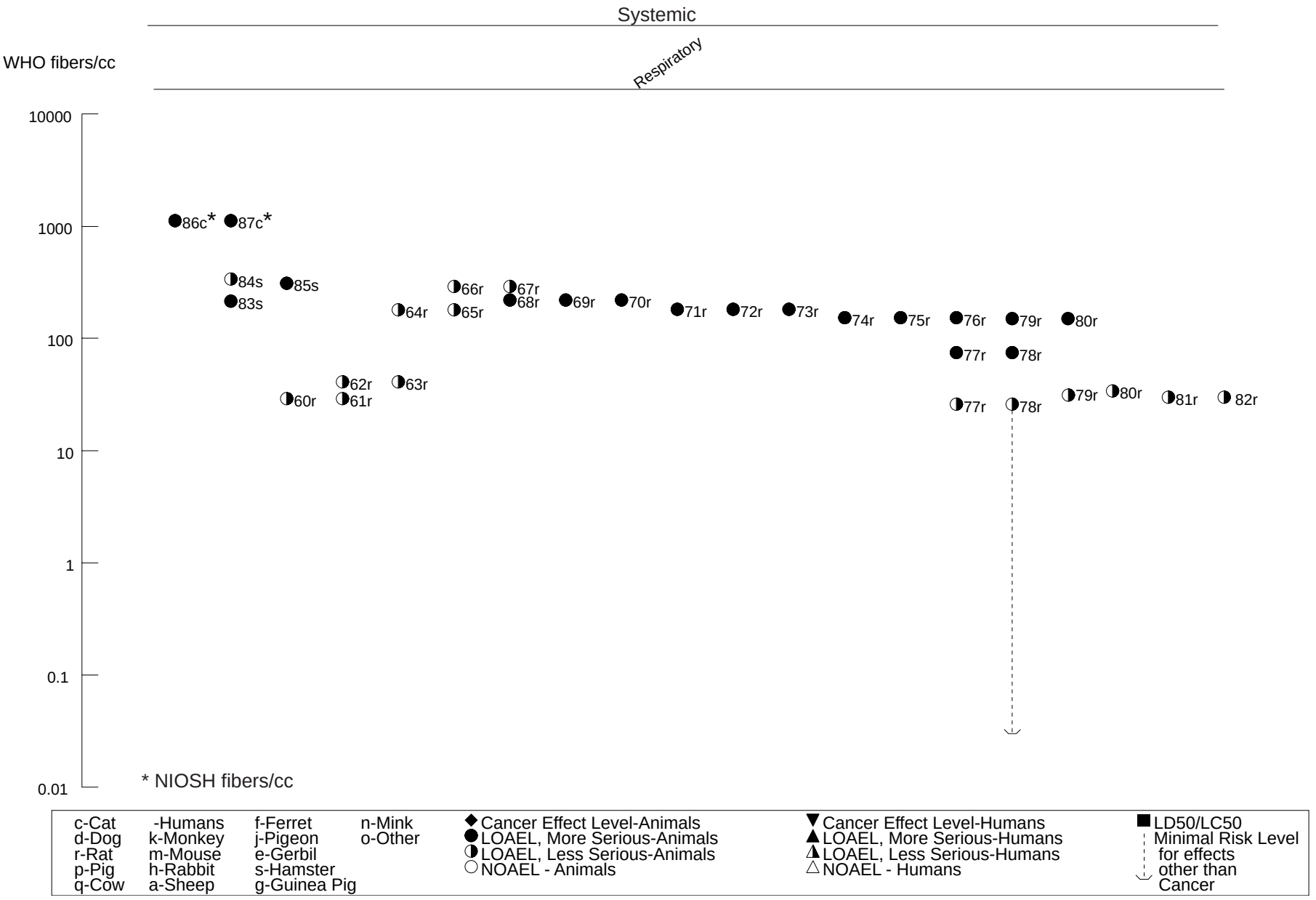


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

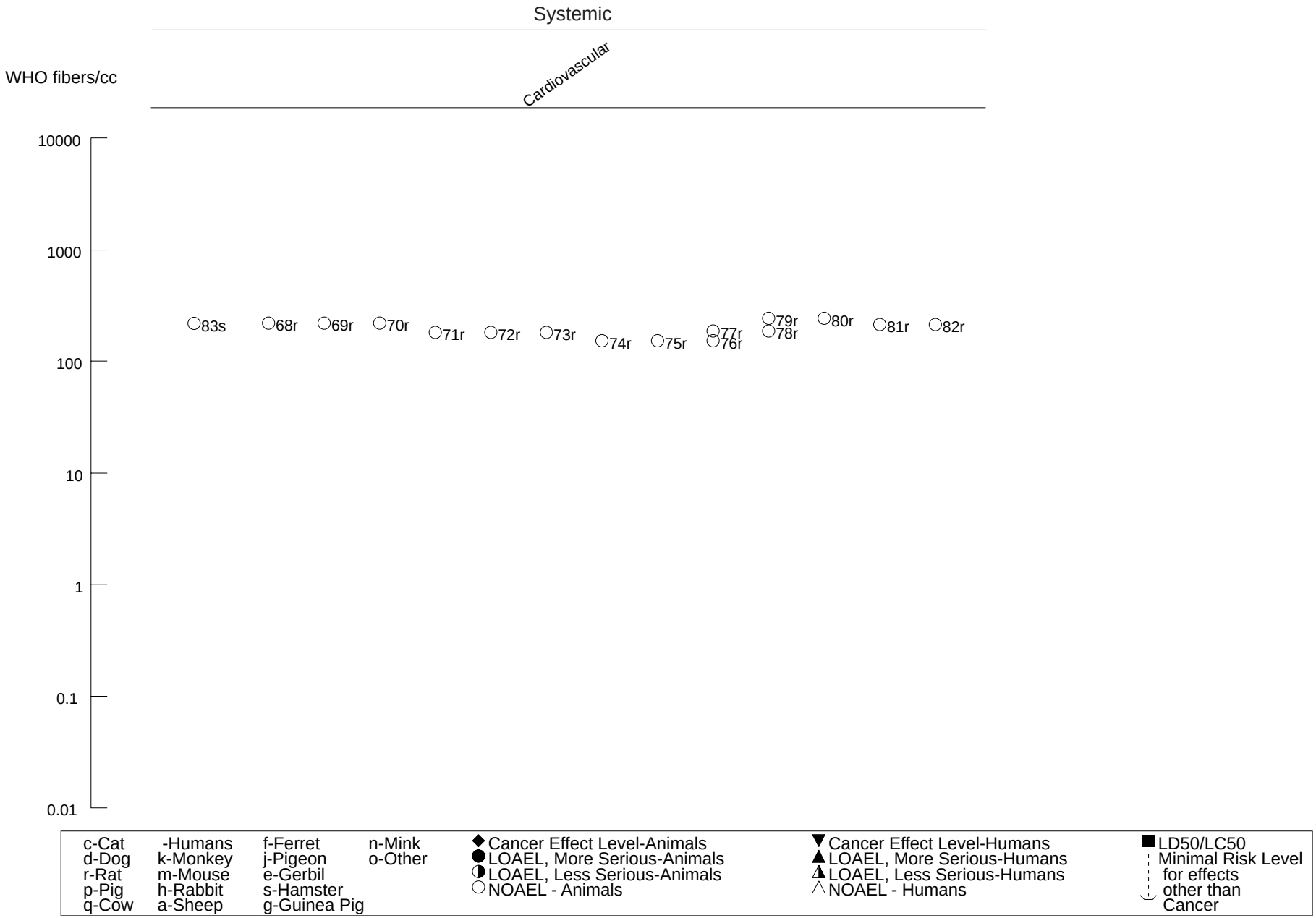


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

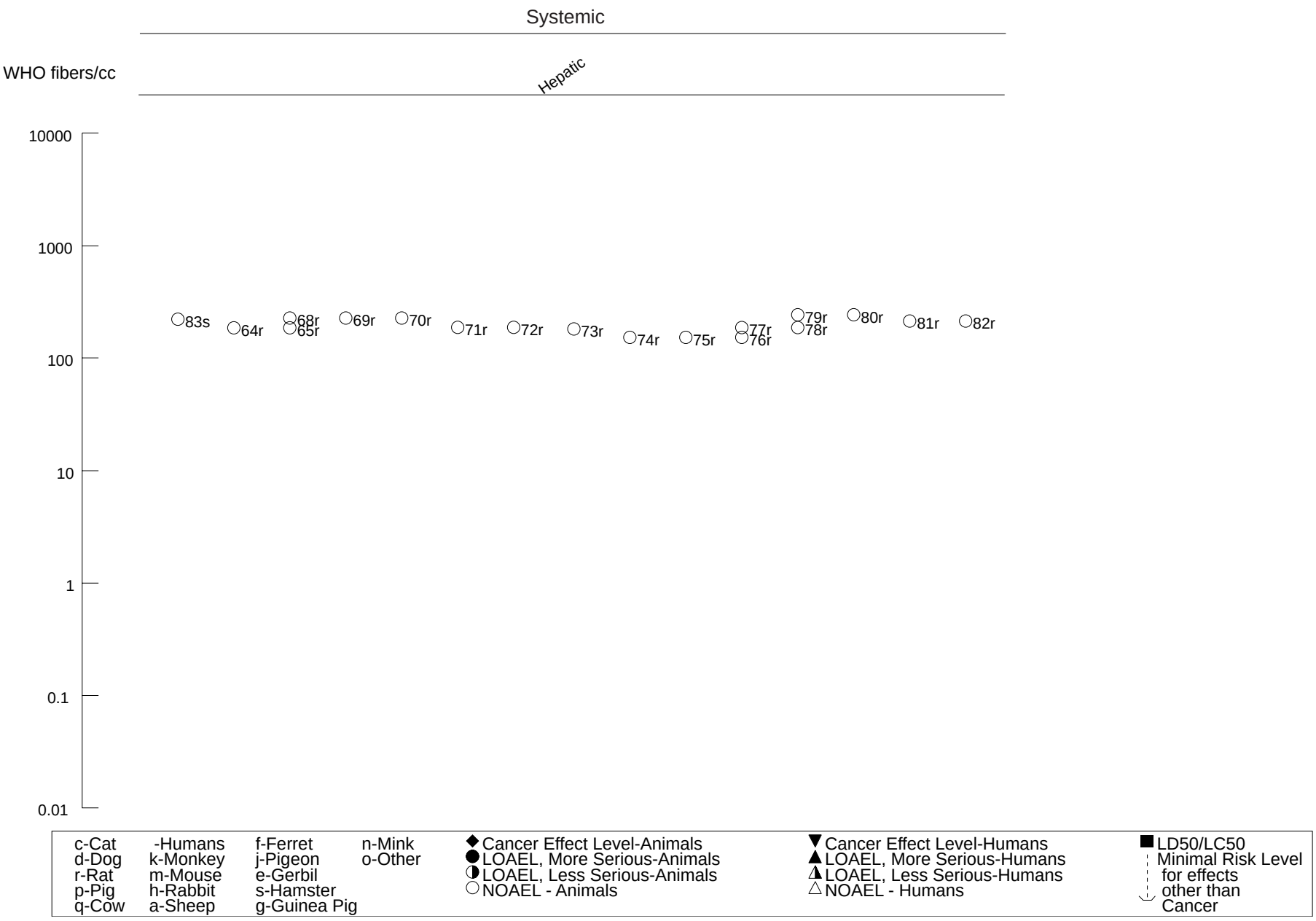


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)

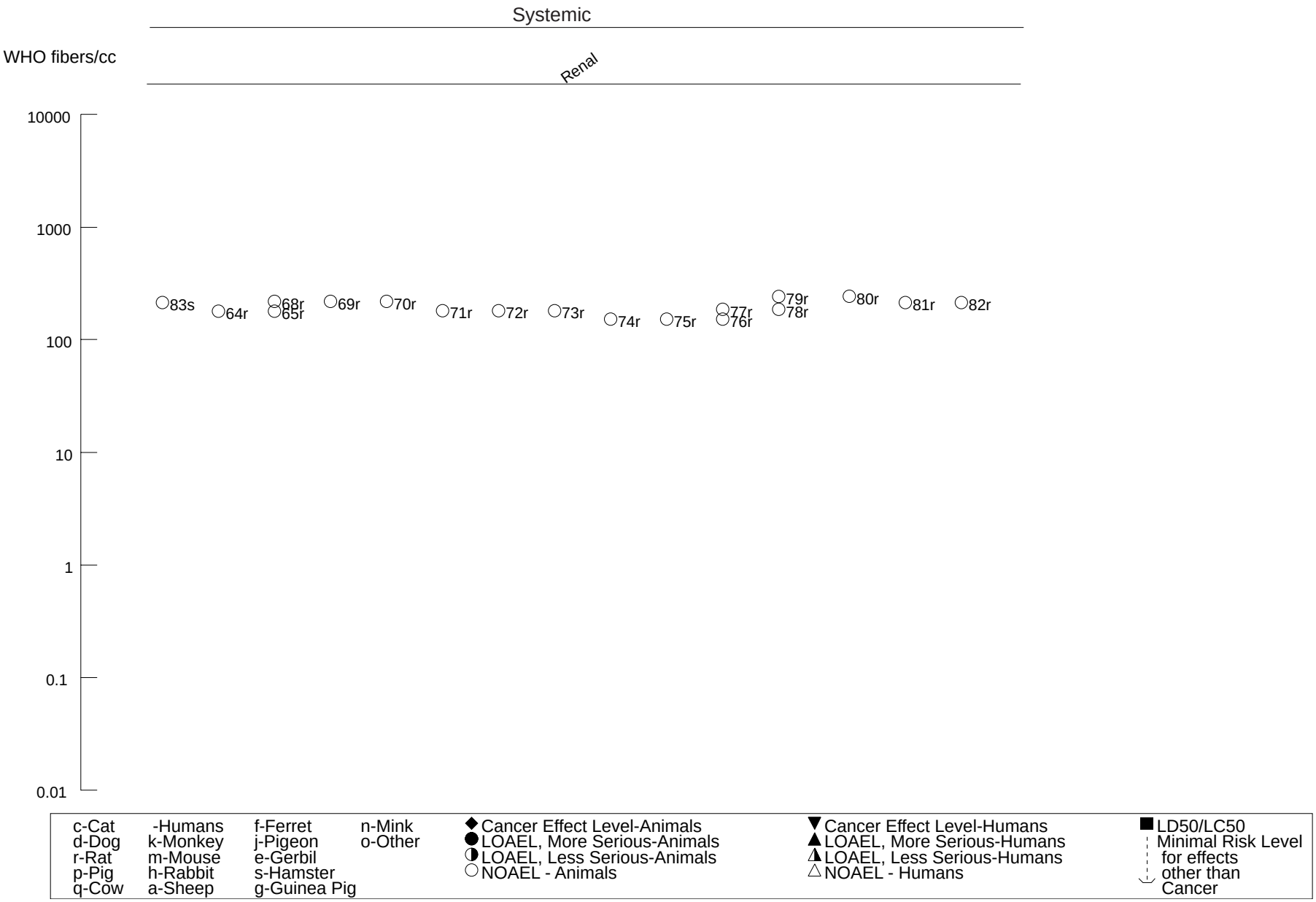
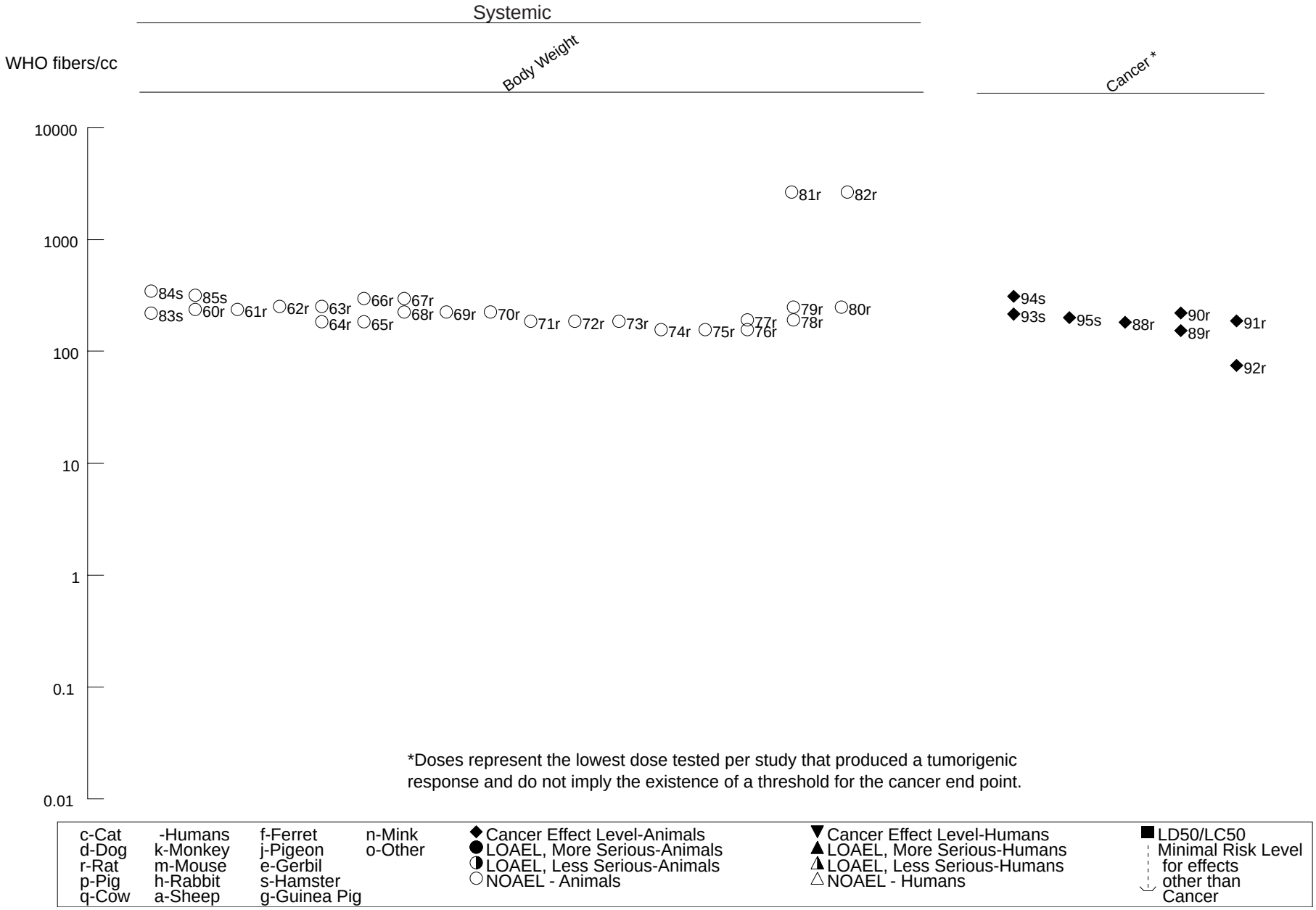


Figure 3-1. Levels of Significant Exposure to Synthetic Vitreous Fibers- Inhalation (*Continued*)

Chronic (≥365 days)



>5 μm, diameter <3 μm, and aspect ratio ≥3:1). To facilitate comparison of effects across studies, this exposure unit is cited in Table 3-1 and Figure 3-1, except for a few studies (Everitt et al. 1994; Goldstein et al. 1983) in which fiber counting measurements were reported only in units using the NIOSH fiber counting rules (i.e., length >5 μm; aspect ratio ≥3:1).

Respiratory Effects.

Human Studies.

Refractory Ceramic Fibers. Research into the health effects of refractory ceramic fibers has been limited by the relatively short time since manufacture began (50 years), small numbers of exposed workers, and confounding exposures (e.g., smoking and asbestos).

Information regarding the effects of acute inhalation exposure to refractory ceramic fibers in humans is limited to a case-report that provided suggestive evidence of respiratory symptoms (cough, eye and throat irritation, wheezing, shortness of breath, and bronchospasm) that required medical treatment following 1 hour of exposure to high levels ("like a snow storm") of refractory ceramic fibers without respiratory protection (Forrester 1997).

No human inhalation studies of intermediate duration (2 weeks–1 year) were located for refractory ceramic fibers.

A low prevalence of pleural plaques (about 3%) has been the most biologically significant effect found in retrospective and longitudinal evaluations of the health of workers involved in the manufacture of refractory ceramic fibers in the United States (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002) and Europe (Cowie et al. 2001). However, consistent statistically significant associations with exposure to refractory ceramic fibers were only found in the U.S. cohort (Lentz et al. 2003; Lockey et al. 1996, 2002). Although diffuse pleural thickening and circumscribed pleural plaques have been associated with impairment of respiratory functions, localized pleural plaques are not thought to be a significant health hazard and have not been mechanistically linked to increased risks of lung fibrosis, lung cancer, or mesothelioma (Agency for Toxic Substances and Disease Registry 2001). Symptoms of dry cough, runny nose, wheezing, and breathlessness also have been reported in European manufacturing workers exposed to refractory ceramic fibers and other dusts (Burge et al. 1995; Trethowan et al. 1995).

Additionally, some studies have observed decreased pulmonary function, usually in exposed workers with histories of smoking (Cowie et al. 2001; LeMasters et al. 1998; Lockey et al. 1998; Trethowan et al. 1995). No fibrosis or other serious health effects have been demonstrated. Although participation rates are high, these studies have been limited by small cohort sizes and relatively short exposure durations. In the only cohort mortality study of refractory ceramic fiber manufacturing workers, there were no statistically significant excesses of death associated with any nonmalignant disease, including nonmalignant respiratory disease (LeMasters et al. 2003).

A U.S. study of 627 current and 220 former refractory ceramic fiber production workers identified pleural changes in 23 men (LeMasters et al. 1994). The pleural changes were classified as plaques for 21 of the cases and thickening for the other 2 cases. Even after adjusting for potential asbestos exposure, a significant association remained between time since first employment and pleural plaques.

A retrospective cohort study of radiographically detected chest changes in 652 workers from five U.S. refractory ceramic fiber plants initially detected 20 cases of pleural plaques (Lockey et al. 1996). In a later report of the survey of radiographic chest changes in U.S. refractory ceramic fiber workers (625 current workers at five plants and 383 former workers at two of the five plants), pleural changes were detected in 27 workers (2.7%) (Lockey et al. 2002). Twenty-two of the cases showed pleural plaques (86% of which were bilateral). In logistic regression analyses that adjusted for asbestos exposure and age, three exposure metrics (duration, time since first employment, and cumulative exposure) showed statistically significant trends for increasing odds ratios with increasing exposure. For example, respective odds ratios (ORs) for pleural changes were OR=2.2 (95% confidence interval (CI) 0.5–11.8), OR=5.6 (95% CI 1.5–28.1), and OR=6.0 (95% CI 1.4–31.0) for the following categories of increasing cumulative exposure (measured in units of fibers-month/cm^3): >15–45, >45–135, and >135. In a similar logistic regression analysis of data collected from the same cohort, odds ratios for pleural plaques showed statistically significant trends with increasing exposure categories for three different cumulative exposure metrics: cumulative exposure; cumulative pulmonary dose of all fibers; and cumulative pulmonary dose of fibers with diameters <0.4 μm and length <10 μm (Lentz et al. 2003). Pulmonary doses for each worker were estimated using air monitoring data from the plants, job histories, and a lung deposition model.

A prospective study of 361 current male U.S. refractory ceramic fiber production workers found a statistically significant (but not biologically significant) decrease in forced vital capacity (FVC) among

workers employed for >7 years at initial testing in 1987 compared to unexposed workers (OR not reported) (Lockey et al. 1998). However, these effects did not remain statistically significant in longitudinal analyses conducted until 1994.

In an initial report of a cohort mortality study of male workers employed at two U.S. refractory ceramic fiber manufacturing plants between 1952 and 2000, no statistically significant excesses were found for deaths by any cause or deaths associated with nonmalignant diseases (LeMasters et al. 2003). A total of 87 deaths were recorded among the 942 men included in the study (9% of the cohort). Eight deaths associated with nonmalignant respiratory disease were recorded, compared with an expected 7.49 deaths based on U.S. mortality rates (standardized mortality ratios [SMR]=107; 95% CI 46–211).

A cross-sectional study of workers from seven European refractory ceramic fiber manufacturing plants showed an association between nasal, skin, and eye symptoms and worker exposure (Burge et al. 1995; Rossiter et al. 1994; Trethowan et al. 1995). A total of 628 employees participated in the study (91% were men). Workplace air monitoring data were available for inspirable dust mass and respirable fibers. In a multiple logistic regression analysis of exposure to inspirable dust and respirable fibers, significantly increased odds ratios for dry cough, dyspnea (grade 2), stuffy nose, eye irritation, and skin irritation were noted for the highest exposure group compared with the lowest exposure group (Burge et al. 1995). No relationships were noted for wheeze or chronic bronchitis with increasing exposure (Burge et al. 1995). When the effects of exposure to inspirable dust mass or respirable fibers were examined as independent variables, the odds ratio was significantly increased only for skin irritation for respirable fibers and for wheeze, dyspnea, and eye irritation for inspirable mass (Burge et al. 1995). A multiple linear regression analysis (which adjusted for confounders such as age) showed that lung function variables in current smokers (forced expiratory volume in 1 second [FEV_1] and forced midexpiratory flow, [FEF_{25-75}]) decreased with increasing cumulative exposure to respirable fibers (Trethowan et al. 1995). Chest x-rays did not show any effects related to exposure to respirable fibers (Trethowan et al. 1995).

In a subsequent cross-sectional morbidity study of 774 ceramic fiber production workers from six European refractory ceramic fiber manufacturing plants, the prevalence of radiographic pleural changes was more strongly related to age and any previous occupational exposure to asbestos than to exposure metrics for refractory ceramic fibers (Cowie et al. 2001). Pleural plaques or pleural changes were noted in 9 or 32 workers, respectively, among the 355 workers without some occupational exposure to asbestos (about 3 or 9%, respectively). In logistic regression analyses that adjusted for age, elevated odds ratios

for pleural plaques or pleural changes were calculated for refractory ceramic workers without asbestos exposure and with >10 years since first exposure to refractory ceramic fibers: OR=2.03 (95% CI 0.78–5.25) for pleural plaques and OR=2.22 (95% CI 1.17–4.24) for pleural changes. Exposure-related changes in pulmonary function variables were restricted to the finding that FEV_1 and FVC in workers who smoked showed decreasing values with increasing measures of exposure.

Glass Wool, Rock and Slag Wool, and Continuous Filament Glass Fibers. In people, acute exposures to fibrous glass materials including continuous glass filament (e.g., fiberglass fabrics), glass wool insulation, and rock and slag wool have been associated with symptoms of upper respiratory tract irritation such as nasal itching and congestion, nosebleed, sore throat, cough, and laryngeal and pharyngeal pain (Horvath 1995; Milby and Wolf 1969; Nasr et al. 1971; Newball and Brahim 1976; Petersen and Sabroe 1991; Thriene et al. 1996). These symptoms have been reported to disappear shortly following cessation of exposure. Upper respiratory tract irritation has been associated mostly with unusually dusty workplace conditions (concentrations >1 fiber/cc) involving removal of fibrous glass materials in closed spaces without respiratory protection (ACGIH 2001; EPA 1980), and similar symptoms of upper respiratory irritation may also occur in workers involved in the manufacture, application, or removal of insulation materials made from rock wool or slag wool (ACGIH 2001).

Reliable data regarding the effects of intermediate (2 weeks–1 year) inhalation exposure of people to continuous glass fibers, glass wool, and rock and slag wool are limited because cross-sectional studies have been limited to workers with longer exposures and cohort studies have frequently been confounded by strong healthy worker effects (Boffetta et al. 1997, 1998, 1999; Lea et al. 1999; Marsh et al. 2001a; Sali et al. 1999; Shannon et al. 1987, 1990).

The possible effects of chronic exposure to continuous glass fibers, glass wool, and rock and slag wool have been investigated in cross-sectional health evaluation studies, cohort mortality studies, and case-control studies. Respiratory symptoms similar to those seen in acute studies (decreased pulmonary function, coughing, bronchitis) have been reported (Albin et al. 1998; Clausen et al. 1993; Engholm and von Schmalensee 1982; Kilburn et al. 1992). Attempts to determine whether or not exposure to continuous glass filament, glass wool, and rock and slag wool induced pleural plaques have been inconclusive or negative (Hughes et al. 1993; Kilburn and Warshaw 1991; Kilburn et al. 1992; Sanden and Jarvholm 1986; Scansetti et al. 1993; Weill et al. 1983). Cohort mortality studies have found no

association between exposure and increased risk for mortality from nonmalignant respiratory disease (Hunting and Welch 1993; Marsh et al. 2001a; Sali et al. 1999; Shannon et al. 1987, 1990).

Cross-sectional studies of populations working with fibrous glass have focused on the prevalence of respiratory symptoms through the administration of questionnaires, pulmonary function testing, and chest x-ray examinations (Clausen et al. 1993; Ernst et al. 1987; Gross 1976; Hansen et al. 1999; Hill et al. 1973; Hughes et al. 1993; Kilburn et al. 1992; Moulin et al. 1988; Nasr et al. 1971; Sanden and Jarvholm, 1986; Weill et al. 1983; Wright 1968). In general, these studies reported no consistent evidence for increased prevalences of adverse respiratory symptoms, abnormal pulmonary functions, or chest x-ray abnormalities (e.g., pneumonia, bronchitis, emphysema, pleural effusion and thickening, solid lesions, and abnormal heart and aorta). However, increased incidences of coughing (Albin et al. 1998) and bronchitis (Engholm and von Schmalensee 1982) among Swedish construction workers exposed to glass and rock wool as well as decreased pulmonary function (forced expiratory volume in 1 second) among Danish construction workers exposed to glass and rock wool (Clausen et al. 1993) and U.S. appliance assembly workers exposed to glass wool (Kilburn et al. 1992) have been observed. These studies did not have data regarding symptoms following cessation of exposure, so the persistence of these symptoms is unknown. In addition, information of exposure levels experienced by these workers was unavailable.

Because occupational exposure to inhaled asbestos has been associated with changes in the pleural membrane (such as plaques, thickening, and fibrosis) (Agency for Toxic Substances and Disease Registry 2001), several cross-sectional studies analyzed chest x-rays of workers exposed to synthetic vitreous fibers but did not find consistent evidence for an association between pleural changes and exposure to fibrous glass, rockwool, or slag wool. No increased incidence of pleural plaques or radiographic densities were seen in a study of 1,401 continuous glass filament and glass wool production workers (Wright 1968) or in a study of 788 male and 145 female rock wool production workers (Jarvholm et al. 1995). An initial cross-sectional study performed in 1979–1980 of U.S. fiberglass and mineral wool workers detected a low prevalence of small lung opacities of low profusion that correlated significantly with duration of employment at two of the seven plants studied (Weill et al. 1983). However, in a follow-up study that used prevalences of opacities in a local population as a control, no excesses of opacities were identified in the exposed workers that were related to fiber exposure (Hughes et al. 1993). Two other studies observed opacities in groups of workers, but did not report data for reference populations, so the results are inconclusive (Kilburn and Warshaw 1992; Kilburn et al. 1992). Lung radiographic abnormalities were seen in 8 of 38 glass wool production workers exposed to fiberglass but not to asbestos and in 23 of

137 workers exposed to both asbestos and fiberglass (Kilburn and Warshaw 1992). A separate study of appliance assembly workers exposed to glass wool observed radiographic abnormalities in 43 of 284 workers (Kilburn et al. 1992). Although 36 of these cases were attributed to fiberglass exposure, the adjustments made for self-reported asbestos exposure and smoking data were unclear (Bender 1993). Other studies observed pleural plaques and cough with phlegm only among fibrous glass workers with reported or suspected co-exposure to asbestos (Sanden and Jarvholm 1986; Scansetti et al. 1993).

Data for mortality from nonmalignant respiratory diseases were analyzed for three major groups of workers involved in the manufacture of workers exposed to filament glass fibers, glass wool, rock wool, or slag wool in the United States (Bayliss et al. 1976; Chiazze et al. 1997, 2002; Enterline and Henderson 1975; Enterline et al. 1983; Marsh et al. 1990, 2001a; Robinson et al. 1982; Wong et al. 1991; Watkins et al. 1997), Europe (Claude and Frentzel-Beyme 1984, 1986; Gustavsson et al. 1992; Lea et al. 1999; Sali et al. 1999; Simonato et al. 1986a; Teppo and Kojonen 1986), and Canada (Shannon et al. 1984, 1987, 1990). These cohort studies (and their associated case-control studies) have the strengths of large sample sizes, long follow-up periods, low losses in follow-up, and use of existing employment records to assess exposure, but have the limitations of imprecise estimations of actual exposure levels and the inability to adjust for confounding from tobacco smoke and concomitant exposure to other hazardous agents in the workplace. (These cohort studies are also discussed in Section 3.2.1.7, Cancer.)

The available cohort studies observed no increased risk of mortality from nonmalignant respiratory diseases in U.S., European, or Canadian workers. Significantly decreased risks of mortality from nonmalignant respiratory disease compared with national rates reported in the U.S. fiberglass cohort (Marsh et al. 2001a) and in the Canadian studies on glass wool (Shannon et al. 1984, 1987) and glass filament (Shannon et al. 1990) workers are consistent with a possible healthy worker effect, but the European cohort study did not find decreased risks (Sali et al. 1999). Categories of nonmalignant respiratory disease considered by these major studies were divided by organ (larynx, bronchus, trachea, and lung) and health effect (including asthma, bronchitis, emphysema, influenza, and pneumonia). Similarly, a cohort of 333 U.S. sheet metal workers investigating obstructive lung disease did not consider exposure to fiberglass as a risk factor (Hunting and Welch 1993).

Animal Studies.

Although many animal studies administering various synthetic vitreous fibers by injection or implantation into the intrapleural or intraperitoneal cavities have reported the development of administration site nonneoplastic and neoplastic lesions (see Section 2.2.4, Other Routes of Exposure), these results are of limited usefulness for predicting health hazards in humans exposed by inhalation. Studies that exposed animals by inhalation to well-measured levels of respirable fibers are considered more appropriate for assessing potential risk to human health.

Studies in rats (Bellmann et al. 2001; Brown et al. 2000; Cullen et al. 2000; Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Haratake et al. 1995; Hesterberg et al. 1993c, 1998b, 1999; Johnson and Wagner 1980; Kamstrup et al. 1998, 2001; Le Bouffant et al. 1987; Lee et al. 1981b; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999; Muhle et al. 1987; Smith et al. 1987; Yokosakai et al. 1991), hamsters (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Hesterberg et al. 1999; Lee et al. 1981b; McConnell et al. 1995; Smith et al. 1987), guinea pigs (Lee et al. 1981b), and baboons (Goldstein et al. 1983) have observed consistent, dose-related responses to the inhalation of synthetic vitreous fibers; and only one study reported a NOAEL for respiratory effects (Muhle et al. 1987; see Figure 3-1). In the lungs, an immediate inflammatory response has been observed in rats and mice at the lowest exposure-levels tested, approximately 30–40 WHO fibers/cc of glass wool (Hesterberg et al. 1993c, 1999), rock wool (McConnell et al. 1994), slag wool (McConnell et al. 1994), and refractory ceramic fibers (Mast et al. 1995a, 1995b). End points used to measure lung inflammation include infiltration of macrophages (which accumulate fibrous and nonfibrous inhaled particles), microgranuloma formation (nonneoplastic focal accumulations of macrophages), increases in other immune cells, and increases in biochemical markers (lactate dehydrogenase, gamma-glutamyl transferase, N-acetylglucose-aminidase, glutathione, fibronectin, and total protein). Although the intensity of inflammatory changes increased with increasing exposure, these effects have subsided rapidly after cessation of exposure and are therefore not considered serious in the absence of other lesions. The reversible pulmonary inflammatory effects observed following repeated inhalation exposure to synthetic vitreous fibers are typical of the lung's response to other relatively water-insoluble particles, both non-fibrous and fibrous particles (Churg et al. 2000; Driscoll 1996; Hesterberg and Hart 2001; Kane 1996; Mossman and Churg 1998). In animal studies where exposure atmospheres included nonfibrous particles (e.g., the studies of the refractory ceramic fiber preparation, RCF1, reported by Mast et al. [1995a, 1995b]), the nonfibrous

particles are expected to have contributed to the observed inflammatory responses to some undetermined degree (Maxim et al. 2003b).

With repeated exposure scenarios to higher concentrations, more serious effects have been seen. Epithelial hyperplasia and alveolar bronchiolization, an epithelial cell transition from flat to cuboidal morphology, have been seen following chronic exposure to concentrations as low as about 180–240 WHO fibers/cc for several types of synthetic vitreous fibers including insulation glass wools (MMVF10, MMVF11; Hesterberg et al. 1993c), refractory ceramic fibers (RCF1, RCF2, RCF 3, RCF4; Mast et al. 1995a, 1995b), and rock and slag wools (MMVF21, MMVF22; McConnell et al. 1994). For some fibers (e.g., refractory ceramic fibers, MMVF21, MMVF33, C102/C104 blend fibrous glass), signs of minimal-to-moderate fibrosis following repeat exposure have been observed (Bellman et al. 2001; Goldstein et al. 1983; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1995, 1999). Severe fibrosis was reported by only one study, with 104E-glass, a specialty continuous glass filament (Cullen et al. 2000). Because no regression has been observed following cessation of exposure, fibrosis is considered a serious respiratory lesion.

Refractory Ceramic Fibers. The nonneoplastic respiratory effects of inhalation exposure to refractory ceramic fibers have been studied in conjunction with carcinogenicity studies (see Section 3.2.1.7, Cancer). In addition to intermediate and chronic studies in both rats and hamsters demonstrating reversible inflammation and irreversible fibrosis (Bellmann et al. 2001; Brown et al. 2000; Everitt et al. 1994, 1997; Gelzleichter et al. 1996a, 1996b, 1996c, 1999; Hesterberg et al. 1998b; Mast et al. 1995a, 1995b; McConnell et al. 1995; Smith et al. 1987; Yokosakai et al. 1991), acute- and intermediate-duration studies have found increased pleural mesothelial cell proliferation following acute and intermediate exposure in both hamsters and rats (Everitt et al. 1994, 1997; Gelzleichter et al. 1999).

Although early rodent inhalation studies provided only limited information regarding the refractory ceramic fiber tested (Smith et al. 1987; Yokosakai et al. 1991), subsequent studies have identified specific types of refractory ceramic fibers: RCF1 is a kaolin-based refractory ceramic fiber (55–75% fiber), RCF1a is a fiber-enriched preparation of RCF1 containing 98% fiber, RCF2 is an aluminum zirconia-based fiber, RCF3 is a high-purity kaolin, and RCF4 is an “after-service” kaolin-based fiber previously exposed to high temperatures. Most studies have focused on RCF1, which is comparable to RCF3 (Mast et al. 1995a) and more toxic than RCF2 or RCF4 (Mast et al. 1995a).

Acute studies are only available for RCF1, and have observed pulmonary and pleural inflammation (Everitt et al. 1994; Gelzleichter et al. 1996a, 1996b, 1996c). In both Fischer 344 rats and male Syrian Golden hamsters exposed nose-only to 1,700 NIOSH fibers/cc of RCF1 (6,900 total particles/cc) for 5 days, end points demonstrating inflammation included increased relative numbers of pulmonary neutrophils (without changing total numbers of lavaged cells in the bronchoalveolar lavage fluid) and increased lung mesothelial cell proliferation; pleural neutrophil frequency was increased only in hamsters (Everitt et al. 1994). Similarly, male Fischer 344 rats exposed to 2,645 WHO fibers/cc of RCF1 (55% fiber; 89 mg/m^3) exhibited pulmonary and pleural inflammation following 5 days of exposure or at 4 weeks postexposure (Gelzleichter et al. 1996a, 1996b). The pulmonary inflammation consisted of a dramatic and transient increase in bronchoalveolar levels of neutrophils, a delayed increase in pleural monocyte and eosinophil numbers, and a sustained (for 4 weeks) increase in bronchoalveolar markers for inflammation (lactate dehydrogenase, N-acetyl glucosaminidase, alkaline phosphatase, total protein, albumin, soluble fibronectin, and leukocyte fibronectin secretion). Pleural inflammation was more limited, and was measured with biochemical markers (increased N-acetyl glucosaminidase and leukocyte fibronectin secretion only immediately after exposure and increased total protein, albumin, and soluble fibronectin only at 4 weeks postexposure).

Intermediate-duration nose-only inhalation experiments with refractory ceramic fibers in male Fischer 344 rats (Mast et al. 1995a, 1995b), female Wistar rats (Bellmann et al. 2001; Brown et al. 2000), and male Syrian Golden hamsters (Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995) have verified the observations of pulmonary and pleural inflammation, and have also shown signs of progressive fibrosis.

In male Fischer 344 rats, concentrations of RCF1 as low as 26 WHO fibers/cc (3 mg/m^3) for 3 months have caused pulmonary inflammation (statistically significant increases in relative lung weight, macrophage infiltration, and microgranuloma [nonneoplastic focal accumulation of macrophages] formation) (Mast et al. 1995a, 1995b). Exposure for the same duration to at least 75 WHO fibers/cc (9 mg/m^3) caused another sign of inflammation, alveolar bronchiolization. Alveolar bronchiolization is a pathologic response in which cells lining the alveoli become cuboidal (i.e., resembling cells lining the bronchioles). No fibrosis was seen in rats exposed to 26 WHO fibers/cc of RCF1; 75 WHO fibers/cc caused minimal-to-mild interstitial fibrosis by 12 months, and 187 WHO fibers/cc of RCF1 caused minimal-to-mild pleural fibrosis by 9 months (Mast et al. 1995a, 1995b). Following cessation of exposure, macrophage infiltration and bronchiolization rapidly regressed, but fibrosis neither progressed

nor regressed. Other studies in male Fischer 344 rats with RCF1 have also reported pulmonary inflammation (statistically significant increases in pleural neutrophil, eosinophil and lymphocyte numbers, and biochemical markers of inflammation [pleural lactate dehydrogenase, N-acetylglucos-aminidase, total protein, and fibronectin]) as well as pleural mesothelial cell proliferation following at least 4 weeks of exposure to 300 WHO fibers/cc (45.6 mg/m^3) (Everitt et al. 1997; Gelzleichter et al. 1999).

Exposure of male Fischer 344 rats to single exposure levels of RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively, equivalent to 30 mg/m^3 for each) for at least 3 months caused pulmonary inflammation (macrophage infiltration and microgranuloma formation, bronchiolization of proximal alveoli) (Mast et al. 1995a). Minimal-to-mild focal pleural fibrosis was induced by RCF2 and RCF3 in as little as 6 months and by RCF4 within 9 months (Mast et al. 1995a).

Pulmonary inflammation and slight interstitial fibrosis were also seen in female Wistar rats exposed to 679 WHO fibers/cc of RCF1 (51.2 mg/m^3) or 481 WHO fibers/cc of RCF1a (25.8 mg/m^3) for 3 weeks (Bellmann et al. 2001; Brown et al. 2000). RCF1a was a preparation of the same material cerused to prepare RCF1, but was prepared so that aerosols made from it contained less nonfibrous particles than RCF1 aerosols. Approximately 25% of the mass of RCF1 was accounted for by nonfibrous particles compared to about 2% in RCF1a. Inflammation consisted of statistically significantly increased relative and absolute lung weight, biochemical markers of bronchoalveolar inflammation (lactic dehydrogenase, gamma-glutamyl transferase, total protein, and glutathione), and bronchoalveolar infiltration by both macrophages and lymphocytes. Histopathological analyses observed slight interstitial fibrosis, bronchio-alveolar hyperplasia, and alveolar histiocytosis. Bronchioalveolar inflammation and hyperplasia subsided within 3 months postexposure, but neither interstitial fibrosis nor alveolar histiocytosis decreased within the 1-year postexposure observation period. Exposure to RCF1 caused a severe retardation of alveolar clearance, but RCF1a did not, suggesting that the effect may have been a nonspecific response to total lung burden.

Intermediate-duration studies with RCF1 in male Syrian Golden hamsters also demonstrated pulmonary inflammation and both interstitial and pleural fibrosis (Everitt et al. 1997; Gelzleichter et al. 1999; McConnell et al. 1995). In hamsters, concentrations as low as 215 WHO fibers/cc (30 mg/m^3) of RCF1 induced a dramatic bronchioalveolar infiltration by macrophages accompanied by the appearance of microgranulomas, and progressive pulmonary and pleural fibrosis (including alveolar bronchiolization,

punctate pleural foci, and collagen deposition) from 3 months onward (McConnell et al. 1995). In the recovery animals (treatment stopped at 3, 6, 9, or 12 months) examined at 18 months, no progression or regression of fibrosis was observed versus comparably-exposed interim sacrifices, although macrophage levels quickly reverted to normal. Male Syrian hamsters exposed to approximately 300 WHO fibers/cc of RCF1 (46 mg/m^3) for as short a duration as 4 weeks also exhibited statistically significant increases in pleural neutrophil, eosinophil, and lymphocyte numbers; biochemical markers of inflammation (pleural lactate dehydrogenase, N-acetylglucosaminidase, total protein, and fibronectin); pleural mesothelial cell proliferation; and visceral pleural collagen levels (Everitt et al. 1997; Gelzleichter et al. 1999).

Chronic studies have observed similar respiratory effects in rats (Hesterberg et al. 1998b; Mast et al. 1995a, 1995b) and hamsters (McConnell et al. 1995; Smith et al. 1987). Male Fischer 344 rats exposed to at least 26 WHO fibers/cc of RCF1 (3 mg/m^3) for 18 or 24 months showed increased lung weight, macrophage infiltration with microgranuloma formation, alveolar bronchiolization, and pleural and interstitial fibrosis (Mast et al. 1995b). Exposure of male Fischer 344 rats to RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively, equivalent to 30 mg/m^3 for each) for 18 or 24 months caused pulmonary inflammation (macrophage infiltration and microgranuloma formation, bronchiolization of proximal alveoli) and minimal-to-moderate interstitial fibrosis and focal pleural fibrosis (Mast et al. 1995a). Exposure to RCF1, RCF2, or RCF3 (but not RCF4) also caused bronchiolar-alveolar hyperplasia

No nonmalignant respiratory effects were reported for male Syrian hamsters or female Osborne-Mendel rats exposed to 200 fibers/cc (12 mg/m^3) of an unspecified refractory ceramic fiber (diameter 1.8 μm) for 2 years, but these results are inconclusive due to data reporting limitations (Smith et al. 1987; this NOAEL is not in Table 3-1 or Figure 3-1). Male Syrian Golden hamsters exposed for 15 or 18 months to 215 WHO fibers/cc (30 mg/m^3) of RCF1 exhibited dramatic pulmonary inflammation (bronchioalveolar infiltration of macrophages, accompanied by the appearance of microgranulomas, alveolar bronchiolization), as well as mild-to-moderate interstitial and pleural fibrosis (McConnell et al. 1995).

Glass Wool (Insulation Glass Wools and Special Purpose Glass Fibers). No acute-duration glass wool inhalation studies in animals were identified.

All but one (Tempstran 475, Code 104 fiber, a special purpose glass fiber) of the glass wools induced pulmonary inflammation in animals following intermediate- or chronic-duration inhalation exposure (Muhle et al. 1987). However, the only glass wools to induce fibrosis were C102/C104 blend fibrous

glass (with chronic- but not intermediate-duration exposure) (Goldstein et al. 1983), and two special purpose glass fibers (with intermediate- and chronic-duration exposures): MMVF33 (McConnell et al. 1999) and 104E-glass (Cullen et al. 2000).

The glass wools best characterized in animal inhalation studies are MMVF10, MMVF11, and MMVF33 (Hesterberg et al. 1993c, 1999; McConnell et al. 1999). MMVF10 and MMVF11 are standard building insulation glass wools, whereas MMVF33 is a more durable special purpose glass fiber. Short-duration multiple-exposure-level studies with MMVF10 in male Syrian Golden hamsters observed minimal pulmonary inflammation (macrophage infiltration and microgranuloma formation) at levels as low as 36 WHO fibers/cc after 13 weeks and 316 WHO fibers/cc after 7 weeks (3.2 and 30.5 mg/m^3, respectively) (Hesterberg et al. 1999). At 13 weeks, additional signs of inflammation were seen at the next-lowest concentration (increased numbers of pleural and pulmonary neutrophils and lymphocytes at concentrations as low as 206 WHO fibers/cc [16.5 mg/m^3]) (Hesterberg et al. 1999). These results are consistent with observations of pulmonary inflammation (macrophage infiltration and microgranuloma formation) in male Wistar rats exposed to the same approximate gravimetric concentration (2.2 mg/m^3; fiber/cc counts not reported) of GB100R glass wool (Haratake et al. 1995) and in male Fischer rats exposed to 29 and 41 WHO fibers/cc (3.1 and 4.8 mg/m^3) of either MMVF10 or MMVF11, respectively (Hesterberg et al. 1993c). No differences between MMVF10 and MMVF11 were observed in the latter experiment; no fibrosis was induced at the highest concentrations tested, 232 and 246 WHO fibers/cc (27.8 and 28.3 mg/m^3), and no progression of effects was seen in animals sacrificed at 18 or 24 months compared to those sacrificed at 12 months.

The other rodent experiment, which included both intermediate and chronic timepoints, tested MMVF10a (a low fluorine preparation of MMVF10) and MMVF33 (a durable special applications glass fiber) for 18 months in male Syrian Golden hamsters at concentrations of 339 or 310 WHO fibers/cc, respectively (29.6 or 37 mg/m^3) (McConnell et al. 1999). Pulmonary inflammation was seen as early as 13 weeks (macrophage infiltration and microgranuloma formation). MMVF10a did not induce fibrosis, but MMVF33 induced mild-to-moderate interstitial and pleural fibrosis as well as other markers of inflammation (increased absolute lung weight; neutrophil, eosinophil, and lymphocyte infiltration; elevated lactate dehydrogenase, beta-glucuronidase, and total protein levels; alveolar bronchiolization), beginning at 13 weeks. Both glass fibers induced mesothelial (but not bronchoalveolar) hyperplasia at 18 months (not measured at previous timepoints).

In male Wistar rats exposed whole-body at 1,022 WHO fibers/cc to 104E-glass or 1,019 WHO fibers/cc of 100/475 glass (two special-purpose glass fibers) for 1 year, both fiber types caused "considerable" pulmonary inflammation (macrophage infiltration associated with alveolar wall thickening), but only 104E-glass produced considerable fibrosis (Cullen et al. 2000). Rats exposed for 1 year to 104E-glass and allowed to recover for an additional year exhibited bronchoalveolar hyperplasia and fibrosis more advanced than in animals sacrificed immediately after exposure. In nine rats exposed to 104E-glass that survived during the "recovery" period, advanced alveolar fibrosis and bronchoalveolar hyperplasia covered an average 8% of lung parenchyma area. In contrast, this lesion covered only 0.2 and 0.08% of lung parenchyma in 100/475-exposed rats and control rats, respectively.

The other intermediate (Goldstein et al. 1983; Johnson and Wagner 1980; Lee et al. 1981b; Muhle et al. 1987) and chronic (Goldstein et al. 1983; Le Bouffant et al. 1987; Smith et al. 1987) studies of other glass wools reported minimal respiratory effects (pulmonary inflammation), but no serious nonneoplastic health effects (such as fibrosis).

The only experiment with glass wool performed in a nonrodent species used baboons (*Papio ursinus*) and was applicable to both intermediate and chronic exposure (Goldstein et al. 1983). A group of 10 male baboons were exposed to 1,122 fibers (with lengths >5 μm)/cc of a C102–C104 blend of fibrous glass (7.54 mg/m^3; 5.80 mg/m^3 respirable) for 35 months with periodic lung biopsies. Pulmonary inflammation was seen at 8 months (pulmonary infiltration by histiocytes, fibroblasts, and giant cells, respiratory bronchiole wall thickening, and occurrences of ferruginous bodies). By 18 months, focal peribronchiolar fibrosis was detected. These results are inconclusive because data were not provided regarding lung fiber burdens and the frequency with which lesions were observed in the exposed and control groups.

No significant respiratory effects were observed in female Wistar rats exposed nose-only to 252 WHO fibers/cc of Tempstran 475 (Code 104) glass fiber for 1 year (Muhle et al. 1987). This study represents the only animal inhalation NOAEL reported for a synthetic vitreous fiber.

Two intermediate studies with unspecified types of glass wool reported cell lysis, suggesting that clearance mechanisms may have been overloaded (Johnson and Wagner 1980; Lee et al. 1981b). Exposure of Fischer rats to 10 mg/m^3 of a glass wool for 50 weeks caused focal fibrosis and pulmonary inflammation (localized bronchiolar and alveolar degeneration and hyperplasia, and lysis of debris-filled macrophages) (Johnson and Wagner 1980). Rats and guinea pigs exposed to 70 fibers/cc of a ball-milled

(7% fiber) glass wool for 3 months exhibited pulmonary inflammation (hyperplasia and lysis of dust-filled lung cells [presumably macrophages], and a very slight increase in the incidence of ferruginous bodies [iron deposits]) that subsided within 6 months (Lee et al. 1981b). Apparently, no inflammation occurred in similarly exposed hamsters, but conclusions could not be drawn from the study due to limited reporting.

A 2-year assay of four types of glass wool in female Osborne-Mendel rats and male Syrian Golden hamsters did not report any signs of nonmalignant respiratory effects (Smith et al. 1987). The results of this study are inconclusive, because reporting of study details was very limited. As such, NOAELs and LOAELs from this study are not included in Table 3-1 or Figure 3-1. The concentrations were 300 or 3,000 fibers/cc of a 0.45 μm diameter glass (0.3 or 3.0 mg/m^3), 100 fibers/cc of a 3.1 μm diameter glass (10 mg/m^3), 10 or 100 fibers/cc of a 5.4 μm diameter glass (1.2 or 12 mg/m^3), and 25 fibers/cc of 6.1 μm diameter glass (9 mg/m^3).

In Wistar rats exposed for 2 years to a glass wool (concentration not specified), the reported signs were "simple alveolar macrophage reactions" and fibrosis (Le Bouffant et al. 1987). These effects were reported for all of the fibers tested (asbestos, glass wool, and rock wool).

Rock Wool. No acute-duration rock wool inhalation studies in animals were identified.

Two parallel studies, with intermediate and chronic timepoints, provide the most reliable information for the respiratory effects of MMVF21 and MMVF34/HT rock wool (Kamstrup et al. 1998, 2001; McConnell et al. 1994). MMVF21 is a traditional basalt-based, rock (stone) wool. MMVF34/HT is a more recently developed rock wool characterized as having a relatively high content of aluminum and low content of silica, compared with MMVF21. Supporting information is provided by an intermediate (Johnson and Wagner 1980) and a chronic (Le Bouffant et al. 1987) study. Pulmonary inflammation was seen for all of the rock wools tested; fibrosis was seen for MMVF21 (and unspecified types of rock wool), but not for MMVF34.

In male Fischer 344 rats exposed nose-only to MMVF21 at concentrations of 34, 150, or 243 WHO fibers/cc (3.1, 16.1, or 30.4 mg/m^3) for up to 24 months with interim sacrifices, minimal pulmonary inflammation (increase in pulmonary macrophages) was seen at levels as low as 34 WHO fibers/cc (3.1 mg/m^3) by 3 months, and severity of the inflammatory response increased with increasing exposure

level (Kamstrup et al. 2001; McConnell et al. 1994). For example, rats in the highest exposure group showed mild bronchiolization, in addition to increased pulmonary macrophages, by 3 months of exposure. Signs of minimal fibrosis (collagen deposition at the bronchoalveolar junction) were found in 2/6 rats exposed to 264 WHO fibers/cc at 12 months of exposure. By 18 months of exposure, all rats exposed to 150 or 264 WHO fibers/cc showed signs of minimal or mild fibrosis (rats with mild fibrosis showed some interlobular linking), but the fibrosis was not more pronounced at these exposure levels after 24 months.

In male Fischer 344 rats exposed nose-only to 291 WHO fibers/cc (30.1 mg/m^3) of MMVF34/HT, for up to 2 years, inflammation (increased absolute and relative lung weight, macrophage infiltration and microgranuloma formation, alveolar bronchiolization) was seen as early as 3 months (Kamstrup et al. 1998, 2001). Minimal bronchoalveolar collagen deposition (a sign of fibrosis) was seen in a few rats at 6 and 18 months, but was not observed in rats exposed for 12 or 24 months. As such, no clear and consistent signs of pulmonary fibrosis were found in rats exposed to 291 WHO fibers/cc of MMVF34/HT for up to 24 months. The results indicate that the newly developed rock wool, MMVF34/HT, is a less potent respiratory toxicant than the traditional rock wool, MMVF21.

Exposure of Fischer rats to 10 mg/m^3 of an unspecified rock wool for 50 weeks reportedly caused focal fibrosis, localized bronchiolar and alveolar degeneration and hyperplasia, and lysis of debris-filled macrophages (Johnson and Wagner 1980).

In Wistar rats exposed for 2 years to a rock wool (concentration not specified), the reported signs were "simple alveolar macrophage reactions" and fibrosis (Le Bouffant et al. 1987). These effects were reported for several fibers tested (asbestos, glass wool, and rock wool) in this study.

Slag Wool. No acute-duration slag wool inhalation studies in animals were identified. Pulmonary inflammation, but no fibrosis, has been reported for slag wool.

Male Fischer 344 rats exposed nose-only for 2 years to levels as low as 33 fibers/cc of MMVF22, a blast-furnace slag wool (30 WHO fibers/cc; 3.1 mg/m^3) exhibited minimal pulmonary inflammation by 3 months (macrophage infiltration, microgranuloma development, and bronchiolization) (McConnell et al. 1994). The severity of these effects increased with increasing concentration and with longer exposure duration. No fibrosis or effects in the pleura were seen at levels up to 213 WHO fibers/cc (29.9 mg/m^3).

Another study reported no fibrosis or bronchoalveolar metaplasia in female Osborne-Mendel rats or male Syrian Golden hamsters exposed for 2 years to 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/m^3) (Smith et al. 1987). This apparent NOAEL was not included in Table 3-1 or Figure 3-1 due to limiting reporting of experimental details and results for this study.

Continuous Filament Glass. No inhalation studies in animals with continuous glass filaments were identified. Because this type of synthetic vitreous fiber most frequently has large diameters that render the fibers nonrespirable (ACGIH 2001; Lee et al. 1995), studies have focused on other routes of exposure (see Section 3.2.4).

Other Fibers. Exposure of male Fischer 344 rats to high-silica synthetic vitreous fiber, X607, at a concentration of 180 WHO fibers/cc (equivalent to 30 mg/m^3), caused pulmonary inflammation (macrophage aggregation by 13 weeks, alveolar bronchiolization by 39 weeks, and macrophage microgranulation as early as 52 weeks), but no evidence of bronchioalveolar or pleural fibrosis even after 2 years of exposure (Hesterberg et al. 1998b). X607 is a high-silica synthetic vitreous fiber with glass-like characteristics, which is produced using processes similar to those used for rock wool, slag wool, and refractory ceramic fibers. It has temperature resistance properties that are intermediate between those of insulation glass wools and refractory ceramic fibers (Hesterberg et al. 1998b).

The highest reliable NOAEL values and all reliable LOAEL values for respiratory effects (and other systemic effects) in animals exposed by inhalation to synthetic vitreous fibers are summarized in Table 3-1 and plotted in Figure 3-1.

Cardiovascular Effects. Analysis of cause-of-death information for 2,758 male workers (from a cohort of 11,373 men) included in the European cohort study found a statistically significant increase in mortality from ischemic heart disease among continuous filament workers (51 of 172 total deaths, standardized mortality ratio (SMR) of 1.22 with a 95% CI=1.06–1.88), but not among workers exposed to glass or rock and slag wool (mean SMRs of 1.05, and 0.97, respectively) (Sali et al. 1999). Among rock and slag wool workers, the trend for increased risk of mortality from ischemic heart disease correlated significantly with age. No elevations of risk for mortality from diseases of the circulatory system or cerebrovascular disease were observed (SMR ranged from 0.99 to 1.22 and from 0.95 to 1.21, respectively). The results from this study do not clearly establish an association between increased risk of

death from ischemic heart disease and occupational exposure during the manufacture of continuous filament glass, due to the lack of measures of confounding influences on ischemic heart disease such as heat, other chemical exposures in the workplace such as carbon monoxide, and physical strain.

The risk of death from cardiovascular diseases related to occupational exposure to continuous glass fibers, glass wool, and rock and slag wool were not increased significantly in either the U.S. cohort study (Marsh et al. 2001a) or the Canadian studies (Shannon et al. 1987, 1990).

Some intermediate- and chronic-duration animal studies conducted routine heart histopathology, but did not find any adverse effects (see Table 3-1).

Gastrointestinal Effects. The majority of synthetic vitreous fibers that are deposited in the respiratory tract during inhalation exposure are transported by mucociliary action to the pharynx, where they are swallowed (see Section 3.4). Consequently, the gastrointestinal epithelium is also directly exposed to fibers as a result of inhalation exposure.

Despite this exposure, inhalation exposure to continuous glass filament, glass wool, and rock and slag wool were not associated with increased risk of mortality from diseases of the digestive tract in the death records of 9,060 workers (from a cohort of 32,110) in the U.S. study (Marsh et al. 2001a), 2,758 male workers (from a cohort of 11,373 men) in the IARC study (Sali et al. 1999), 157 insulating glass wool workers (from a cohort of 2,557) in Sarnia, Canada (Shannon et al. 1984, 1987), 96 continuous glass filament workers (from a cohort of 1,465) in Guelph, Canada (Shannon et al. 1990), or 554 prefabricated houses builders (from a cohort of 1,068) in Sweden with glass and rock wool exposure (Gustavsson et al. 1992).

Some intermediate- and chronic-duration animal studies did not find any adverse histopathologic changes in the gastrointestinal tracts (see Table 3-1).

Hepatic Effects. The European cohort study reported that mortality from cirrhosis of the liver was significantly increased among continuous filament workers (12 of 172 total deaths, SMR=2.12, 95% CI=1.10–3.71), but not among workers exposed to glass or rock and slag wool (mean SMRs of 0.99 and 1.10, respectively) (Sali et al. 1999). The cause for this slight increase is unclear, but may be related to confounding factors related to lifestyle. Cause-of-death information for 2,758 workers (from a cohort of

11,373 men) was analyzed. In contrast, the number of mortalities caused by liver cirrhosis was significantly decreased among the total U.S. cohort compared to national (but not local county) rates (SMRs of 0.68 and 0.88, respectively) (Marsh et al. 2001a). A smaller study analyzing 554 deaths from a cohort of 1,068 prefabricated house builders found no correlation between liver cirrhosis and exposure to glass and rock wool (Gustavsson et al. 1992).

Some intermediate- and chronic-duration animal studies conducted routine liver histopathology but did not report any adverse effects (see Table 3-1).

Renal Effects. No relationship between occupational exposure to rock and slag wool, glass wool, or continuous filament and mortality from nonmalignant renal disease has been detected in occupational cohort studies in the United States (Marsh et al. 2001a), European (Sali et al. 1999), or Swedish (Gustavsson et al. 1992) cohorts. Data for mortality from nonmalignant renal disease were not reported for the Canadian cohorts (Shannon et al. 1987, 1990).

Some intermediate- and chronic-duration animal studies conducted routine kidney histopathology, but did not find any adverse effects (see Table 3-1).

No reliable studies were located regarding the following effects in humans or animals after inhalation exposure to synthetic vitreous fibers:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

The principal target organs of concern for cancer are the lungs (bronchoalveolar adenoma and carcinoma) and the pleura (mesothelioma). Single layers of mesothelial cells compose the pleura, the delicate serous membrane that covers the lungs (visceral pleura) and chest wall and diaphragm (parietal pleura), as well

as the peritoneum, the membrane lining the abdominal walls and viscera. Mesotheliomas are rare malignant tumors of mesothelial cells; their incidence in the general human population is low, and pleural mesotheliomas have not been observed in control animals.

Available epidemiological results provide inadequate evidence of the carcinogenicity of synthetic vitreous fibers in humans (see below). Animal studies have detected elevated incidences of lung tumors and the formation of mesotheliomas following exposure to refractory ceramic fibers and two other fiber types (e.g., special-purpose glass microfiber 104E-glass and MMVF33, a durable special purpose glass fiber), but not for other synthetic vitreous fibers, such as traditional building insulation glass wools, that are less biopersistent (see below and Section 3.5).

Intermediate-duration (1-year) exposure of male Wistar rats to special purpose 104E-glass fibers was associated with a statistically significant increase in the combined (but not individual) incidence of lung adenomas and carcinomas (Cullen et al. 2000). Chronic exposure of male Fischer 344 rats to refractory ceramic fibers, RCF1 or RCF3, was associated with statistically significant elevations in lung adenoma and carcinoma incidence, and exposure to RCF2 was associated with increased lung carcinoma (but not adenoma) incidence (Mast et al. 1995a). In contrast, RCF1 did not induce lung tumors in male Syrian Golden hamsters (McConnell et al. 1995). The discrepancy between the two studies may be related to species specificity or differences in exposure duration (24 months for rats, 18 months for hamsters). No increased lung tumor incidence was reported in intermediate-duration studies with 100/475 special-purpose glass microfiber (Cullen et al. 2000), Code 104/475 special purpose glass fiber (Muhle et al. 1987), or GB100R glass wool (Haratake et al. 1995) in rodents or in chronic-duration studies with MMVF10, MMVF11 (Hesterberg et al. 1993c), MMVF21, MMVF22 (McConnell et al. 1994), MMVF33 (McConnell et al. 1999), MMVF34 (Kamstrup et al. 2001), or X607 fiber (Hesterberg et al. 1998b) in rodents or with C102/C104 blend fibrous glass in baboons (Goldstein et al. 1983).

Only one study has observed a statistically significant increase in pleural mesotheliomas, in male Syrian Golden hamsters exposed to 215 WHO fibers/cc of RCF1 for 18 months (42/102 versus 0/106 for controls) (McConnell et al. 1995); mesotheliomas were first seen at 40 weeks. Other studies have detected one or two mesotheliomas per treatment group among rats exposed to 1,022 WHO fibers/cc of 104E-glass for 1 year (Cullen et al. 2000), rats exposed for 2 years to 75 or 220 (but not 120) WHO fibers/cc of RCF1, as well as RCF2, RCF3, or RCF4 (220, 182, or 153 WHO fibers/cc, respectively)

(Mast et al. 1995a, 1995b), and hamsters exposed to 310 WHO fibers/cc of MMVF33, a durable special purpose glass fiber, for 18 months (McConnell et al. 1999).

Human Studies.

Refractory Ceramic Fibers. In a recent initial report of a cohort mortality study of male workers employed at two U.S. refractory ceramic fiber manufacturing plants between 1952 and 2000 (LeMasters et al. 2003), the only statistically significant excess mortality was deaths associated with cancer of the urinary system. As of December 31, 2000, a total of 87 deaths were recorded among the 942 men (average age=51 years) included in the study (about 9% of the cohort). Observed number of deaths and SMRs for selected cancer-related deaths were as follows (with 95% CI noted in parentheses): all cancers, 29 deaths, SMR=94.2 (63–135); malignancies of the respiratory system, 9 deaths, SMR=78.8 (36–150); and malignancies of the urinary system, 5 deaths, SMR=344.8 (112–806). No mesotheliomas were identified among the cohort to date, based on careful review of death certificates, medical records, and lung tissue analysis. LeMasters et al. (2003) noted that the finding for excess urinary cancer deaths may be a chance finding given the wide confidence interval for the SMR, the large number of statistical tests that were conducted (n=46), and the lack of a plausible mechanistic explanation of how fibers may increase the risk for urinary cancer mortality. Continued monitoring of the mortality experience of this cohort is planned.

Glass Wool, Rock and Slag Wool, and Continuous Filament Glass Fibers. Major cohort mortality and nested case-control studies of groups of workers engaged in the production of filament glass fibers, glass wool, rock wool and slag wool are ongoing in the United States (Bayliss et al. 1976; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Quinn et al. 2001; Robinson et al. 1982; Smith et al. 2001; Stone et al. 2001; Watkins et al. 1997; Wong et al. 1991; Youk et al. 2001) and Europe (Andersen and Langmark 1986; Bertazzi et al. 1986; Boffetta et al. 1997, 1999; Claude and Frentzel-Beyme 1984, 1986; Khaerheim et al. 2002; Lea et al. 1999; Olsen and Jensen 1984; Olsen et al. 1986; Plato et al. 1995c; Sali et al. 1999; Saracci et al. 1984; Simonato et al. 1986a, 1987; Teppo and Kojonen 1986; Westerholm and Bolander 1986). Smaller studies have been conducted in Canada (Shannon et al. 1984, 1987, 1990), Sweden (Gustavsson et al. 1992; Plato et al. 1997), and the United States (Bayliss et al. 1976; Enterline and Henderson 1975; Morgan 1981; Robinson et al. 1982). These studies provide inadequate evidence of carcinogenicity in humans with occupational exposure. Although some small, statistically significant

elevations in respiratory system cancer risk were detected, the lack of sufficient data regarding potential confounding factors prevents a conclusive determination that the increased risks were due to these synthetic vitreous fibers (see below).

Early studies of U.S. fibrous glass production workers did not associate exposure to fibrous glass or rock and slag wool with increased risk of respiratory or other cancers (Bayliss et al. 1976; Enterline and Henderson 1975; Morgan 1981; Robinson et al. 1982), but lacked statistical power due to their small size (cohorts of <1,500 men and cause-of-death information obtained for <400 workers). A larger study analyzed mortality statistics for workers from 17 U.S. plants manufacturing either fiberglass (glass wool or continuous filament glass) or rock wool and slag wool from the 1940s to the 1980s; it was conducted by the University of Pittsburgh under the sponsorship of the Thermal Insulation Manufacturers Association (TIMA), analyzing mortality statistics from the 1940s to the 1980s (Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline 1990; Enterline et al. 1983, 1987; Marsh et al. 1990; Watkins et al. 1997; Wong et al. 1991); the results found either none or small and occasionally statistically significant elevations in the risk for respiratory system cancer among glass wool and rock and slag wool workers, but observed no correlation between length of exposure and increased risk. To overcome limitations in these initial studies, a comprehensive surveillance of the U.S. cohort was performed by the University of Pittsburgh under the sponsorship of the North American Insulation Manufacturer's Association (NAIMA) (Buchanich et al. 2001; Marsh et al. 2001a, 2001b, 2001c; Quinn et al. 2001; Smith et al. 2001; Stone et al. 2001; Youk et al. 2001). Mortality data collected until 1992 for 9,060 workers from a cohort of 32,110 workers in the 10 largest and longest-operating factories were analyzed (Marsh et al. 2001a). The mean exposure to respirable fibers was estimated at 0.073 fibers/cc. A small, but statistically significant, increase in the SMR for respiratory system cancer was limited to workers employed <5 years (SMR=1.12, 95% CI=1.01–1.24), suggesting an exposure-independent "healthy worker" effect. No patterns or statistically significant trends associated increasing risk for respiratory system cancer mortality with increasing measures of exposure (years of employment or estimated cumulative exposure). A nested-case control analysis (632 cases, 572 controls) did not observe any relationship between respiratory system cancer risk and exposure indices (Marsh et al. 2001a; Youk et al. 2001).

The IARC began a large international cohort study of European workers involved in the manufacture of synthetic vitreous fibers in 1976. The study includes 13 factories that produced glass wool, continuous glass filament, or rock and slag wool in Denmark, Finland, Norway, Sweden, the United Kingdom, Germany, and Italy. Early reports frequently focused on data from single countries (Andersen and

Langmark 1986; Bertazzi et al. 1986; Claude and Frentzel-Beyme 1984, 1986; Olsen and Jensen 1984; Olsen et al. 1986; Plato et al. 1995c; Teppo and Kojonen 1986; Westerholm and Bolander 1986) going back as far as the 1930s. The ongoing European study has incorporated these data and has published follow-up reports for data collected through the 1980s (Boffetta et al. 1992; Gardner et al. 1986, 1988; Saracci et al. 1984; Simonato et al. 1986a, 1987) and early 1990s (Lea et al. 1999; Sali et al. 1999), with the most recent reports considering data up to 1995 (Boffetta et al. 1997, 1999). Most recently, cause-of-death information for 4,521 workers (191 continuous filament workers from two factories, 1,679 glass wool workers from five factories, and 1,281 rock and slag wool workers from seven factories) was analyzed from a cohort of 22,002 individuals (Boffetta et al. 1997). No increased risk of cancer incidence was clearly related to exposure, and none were related to duration of employment or time since first employment. Among glass wool workers, a statistically significant overall increase (SMR=1.27, 95% CI=1.07–1.50) in mortality from cancers of the trachea, bronchus, and lung did not persist either when local mortality rates were used or when workers with <1 year of employment were excluded (a national healthy worker effect). The increase of mortality from lung cancer among continuous filament workers (SMR=1.11, 95% CI=0.61–1.86) was not significant overall and was attributed to one factory in Italy. Potential exposure to asbestos was associated with a significant increase (SMR=1.69, 95% CI=1.22–2.29) in the risk of lung cancer among all workers. A statistically significant increase (SMR=1.34, 95% CI=1.08–1.63) in the SMR for risk of death from cancers of the trachea, bronchus, and lung for all rock and slag wool workers was attributed to one factory in Germany where exposure to asbestos was reported. After exclusion of that factory, no significant elevation in risk remained (SMR=1.16, 95% CI=0.87–1.51) for rock and slag wool workers. The authors concluded that “these results are not sufficient” to conclude that exposure to synthetic vitreous fibers increased the risk of lung or other cancer types.

Because cancer incidence may be a more sensitive tool than mortality incidence for the detection of adverse health effects, a cancer incidence study of the European cohort was conducted (Bofetta et al. 1999). Data were obtained from the national cancer registrations of Denmark, Finland, Norway, and Sweden for 3,685 rock and slag wool workers and 2,611 glass wool workers who had been employed for at least 1 year in one of nine factories in between 1933 and 1995. Although the elevation for cancers of the oral cavity and pharynx was statistically significant (27 cases, standard incidence ratio [SIR]=1.84, 95% CI=1.22–2.68) for slag wool workers, the combined incidence of cancers of the oral cavity, pharynx, and larynx combined was not significant (31 cases, SIR=1.46, 95% CI=0.99–2.07). Among glass wool workers, these incidences were not significantly elevated (11 cases, SIR=1.31, 95% CI=0.65–2.34 and 16 cases, SIR=1.41, 95% CI=0.80–2.28, respectively) but the trend between increasing time since first

employment working with glass wool and increased incidences of oral, pharyngeal, and laryngeal cancers was statistically significant. The authors concluded that these data were inadequate evidence of carcinogenicity because potential effects from confounding factors such as smoking had not been included.

In a nested case-control study of 133 lung cancer cases and 513 matched controls among men who worked in seven rock and slag wool manufacturing plants in Denmark, Norway, Sweden, or Germany, no statistically significant associations with exposure were found (Kjaerheim et al. 2002). Occupational exposure was assessed on the basis of interview data and exposure information from the manufacturing plants; cases and controls were placed in quartile categories of exposure. Smoking-adjusted odds ratios for workers with at least 15 years since first exposure showed no evidence of increasing odds ratio with increasing category of cumulative exposure; odds ratios for the second, third, and fourth quartiles of cumulative exposure (with 95%CI noted in parentheses) were 1.3 (0.7–2.3), 1.0 (0.5–1.9), and 0.7 (0.3–1.3), respectively. Similar results were obtained with other exposure metrics and after controlling for other potential confounders.

Two mortality studies were conducted in Canada, using mortality data collected from the national Vital Statistics and Disease Registry. An initial (Shannon et al. 1984) and follow-up (Shannon et al. 1987) study obtained information for 157 male workers employed between 1955 and 1977 for at least 90 days at an insulating glass wool manufacturing plant in Sarnia, Ontario, Canada. In 1978, the mean concentration of glass wool fibers with diameters <3.5 μm in the plant was 0.1 fiber/cc, but the authors believed that earlier concentrations had been higher. A statistically significant increase (SMR=1.99, 95% CI=1.28–3.11) for mortality from lung cancer was detected among exposed employees based on an observed 19 deaths versus 9.5 expected. However, four of these deaths occurred in men with <1 year of exposure, and cancer risk was not elevated in people with at least 5 years of exposure. Because increasing length of exposure did not correlate with increasing risk or decreased latency, the authors considered the results inconclusive. The other mortality study identified 96 deaths from a cohort of workers who had been employed for at least 1 year between 1951 and 1986 at a glass filament plant in Guelph, Ontario, Canada (Shannon et al. 1990). The mean number of fibers in dust samples collected at that plant between 1979 and 1987 reportedly ranged from 0.02 to 0.5 fibers/cc with values as high as 0.91 fibers/cc, but the proportion of glass fibers was not determined. No significant difference in lung cancer mortality was seen. For both Canadian studies, no other differences in cancer mortality incidence were significant (all

cancers combined, cancer of the digestive system and peritoneum, cancer of the genito-urinary organs, lymphatic and hepatopoietic malignancies), and data were not adjusted for smoking habits.

European case-control studies of lung cancer, multiple myeloma, mesothelioma, and cancers of the larynx and hypopharynx conducted separately from the European cohort mortality study have been inconclusive due to relatively few cases exposed to synthetic vitreous fibers without confounding exposures (Brueski-Hohlfeld et al. 2000; Lee et al. 2003; Marchand et al. 2000; Pohlabeln et al. 2000; Rodelsperger et al. 2001). Exposure was estimated by employment information collected from questionnaires, and the potential for co-exposure to asbestos was a confounding factor. An analysis of pooled lung cancer incidence data collected in Germany (1988–1993 and 1990–1996) identified only 51 cases and 28 matched controls (identified from a national mandatory registry of residents) who had been exposed to glass wool or mineral wool (as insulators in the construction industry) without asbestos co-exposure (Brueski-Hohlfeld et al. 2000; Pohlabeln et al. 2000); after adjustment for smoking, this difference was not statistically significant (OR=1.56, 95% CI=0.92–2.65). No statistically significant association between occupational exposure to mineral wool and multiple myeloma was found in a case-control study of 446 cases of multiple myeloma among Swedish construction workers (Lee et al. 2003). A German case-control study for mesothelioma was inconclusive because only two cases of diffuse malignant mesothelioma and two controls (matched from a national mandatory registry of residents) who had been exposed to synthetic mineral fibers, but not asbestos, were identified from a total of 125 cases and 125 controls (Rodelsperger et al. 2001). A French case-control study for squamous cell carcinoma of the larynx or hypopharynx did not associate exposure to exposures to mineral wool (OR=1.33, 95% CI=0.91–1.95 and OR=1.55, 95% CI=0.99–2.41), glass filaments (OR=0.44, 95% CI=0.15–1.31 and OR=0.91, 95% CI=0.30–2.76), or ceramic fibers (OR=1.28, 95% CI=0.51–3.22 and OR=0.78, 95% CI=0.26–2.38) to increased risks of these cancers in 528 cases and 205 controls (hospital patients with nonmalignant respiratory disease) (Marchand et al. 2000).

Small studies of exposure in other occupations have also been inconclusive. A cohort study of 1,342 unexposed workers and 1,068 workers exposed to glass and rock wool in the production of prefabricated houses in 11 Swedish plants did not detect any statistically significant elevation in risk of mortality from any type of cancer (Gustavsson et al. 1992). The study assigned three categories of exposure: the mean for 478 men was 0.11 fibers/cc (range 0.05–0.17 fibers/cc), for 375 men was 0.09 fibers/cc (range 0.05–0.13 fibers/cc), and for 215 men was 0.06 fibers/cc (range 0.02–0.08 fibers/cc). Another cohort study of 2,807 workers (including 478 insulators, the occupation with highest exposure)

in the Swedish prefabricated house industry observed no increased risk of lung cancer (for the general cohort, SMR=0.56, 95% CI=0.45–1.44; for insulators, SMR=0.85, 95% CI=0.01–3.01) associated with exposure to synthetic vitreous fibers (not specified, presumably glass wool) (Plato et al. 1997). The mean exposure to synthetic vitreous fibers (not specified, presumably glass wool) was 0.14 fibers/cc; insulators, as high as 0.18 fibers/cc (Plato et al. 1997).

In summary, studies of workers involved in the manufacture of continuous glass filament, glass wool, and rock and slag wool provide inadequate evidence for carcinogenicity in humans. A number of reviews of the fibrous glass cohort mortality and case-control studies concur with this conclusion (ACGIH 2001; Hesterberg and Hart 2001; IARC 1988, 2002; Lee et al. 1995; NIOSH 1977; NRC Subcommittee on Manufactured Vitreous Fibers 2000; Wilson et al. 1999). No evidence has associated inhalation exposure to these materials with nonrespiratory cancers.

Animal Studies.

Refractory Ceramic Fibers. Studies conducted in rats and hamsters have associated inhalation exposure to refractory ceramic fibers with mesothelioma formation and increased incidences of lung adenomas and carcinomas (Davis et al. 1984; Hesterberg et al. 1998b; Mast et al. 1995a, 1995b; McConnell et al. 1995; Smith et al. 1987).

Two studies relevant to intermediate-duration exposure were identified. Exposure of Wistar rats to 95 WHO fibers/cc of a ceramic aluminum silicate glass for 12 months followed by a 20-month observation period was associated with a statistically significant increase in the combined incidence of respiratory tumors (one adenoma, three carcinomas, and four malignant histiocytomas in a group of 48 rats) compared to controls (no observed tumors in 40 rats) (Davis et al. 1984). Additionally, one peritoneal mesothelioma was identified; the relevance of this tumor outside the pleural cavity is unclear, but it might represent a metastasis of an occult lesion. A chronic study that exposed male Syrian Golden hamsters exposed to 215 WHO fibers/cc (30 mg/m^3) of RCF1 for up to 18 months detected mesotheliomas in animals that reportedly died from other (noncancer) causes: 2 at 40 weeks, 1 at 45 weeks, and 1 at 47 weeks (McConnell et al. 1995). Additionally, a mesothelioma (1/3) was observed in the interim-sacrifice group euthanized at 12 months (McConnell et al. 1995). At study termination, no lung adenomas or carcinomas were seen in control or exposed animals (0/106, 0/102). However, the

incidences of mesothelial cell hypertrophy (0/106 versus 33/102) and pleural mesothelioma (0/106 versus 42/102) were significantly increased.

Other chronic studies have also found evidence of carcinogenicity. No lung tumors were seen in male Fischer 344 rats exposed nose-only to RCF1 at concentrations as high as 120 WHO fibers/cc (17 mg/m^3) for 2 years, although a single mesothelioma was seen at 75 WHO fibers/cc (Mast et al. 1995b). A companion 2-year study exposed male Fischer 344 rats nose-only to single concentrations of RCF1, RCF2, RCF3, or RCF4 (187, 220, 182, or 153 WHO fibers/cc; 30 mg/m^3 for each) (Mast et al. 1995a). The first three concentrations induced statistically significant increases in the incidences of bronchiolar-alveolar hyperplasia (control 5/130; 17/123, 15/121, 15/121, and 8/118 for RCF1, RCF2, RCF3, and RCF4, respectively) and pulmonary carcinoma (control 0/130; 8/123, 5/121, 9/121, and 2/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Only RCF1 and RCF3 significantly induced pulmonary adenomas (control 2/130; 8/123, 5/121, 9/121, and 2/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Although the incidences were not statistically significant, mesotheliomas were detected for RCF1, RCF2, and RCF3 (but not RCF4) (control 0/130; 2/120, 3/123, 2/121, 0/118 for RCF1, RCF2, RCF3, and RCF4, respectively). Data from the 2-year bioassays with male Fischer 344 rats exposed to RCF1 (Mast et al. 1995a, 1995b) provide the best available data describing exposure-response relationships for cancer and chronic exposure to refractory ceramic fibers; however, the presence of non-fibrous particles in the RCF1 test atmosphere is widely acknowledged to have added to the noncancer and cancer responses to an undetermined degree (Bellmann et al. 2001; Mast et al. 2000; Maxim et al. 2003b). Under conditions in which lung clearance mechanisms become overloaded, many types of nonfibrous or fibrous materials can produce pulmonary fibrosis or tumors in rats (Oberdörster 1994).

A mesothelioma was also found in male Syrian Golden hamsters exposed to 200 fibers/cc (12 mg/m^3) of an unspecified type of refractory ceramic fiber for 2 years (Smith et al. 1987). No lung tumors were observed in these hamsters, or in similarly-treated female Osborne-Mendel rats. The study was inconclusive because the positive control (crocidolite asbestos) failed to induce lung tumors and reporting of experimental details was limited.

In summary, different samples of refractory ceramic fibers induced lung tumors in rats and meso-theliomas in both hamsters and rats. These results have demonstrated the carcinogenicity of refractory ceramic fibers in animals following inhalation exposure, and indicate that fiber type and exposure levels are important factors influencing carcinogenicity. It should be noted that the degree to which nonfibrous

particles in RCF1 may have contributed to the carcinogenic responses in RCF1-exposed rats (Mast et al. 1995a, 1995b) is undetermined.

Glass Wool (Insulation Glass Wools and Special Purpose Glass Fibers). Mesothelioma formation has been found in one chronic rat study with MMVF33, a durable special purpose glass fiber (Hesterberg et al. 1999) and another rat study involving 1-year exposures to special purpose 104E-glass fiber (Cullen et al. 2000). No mesotheliomas were found in rats exposed to the insulation glass wools, MMVF10 or MMVF11 (Hesterberg et al. 1993), or in hamsters exposed to MMVF10a (McConnell et al. 1999). Exposure to special purpose 104E-glass fiber also induced increased incidences of lung tumors in rats (Cullen et al. 2000). In contrast, inhalation studies with MMVF33 and the insulation glass wools, MMVF10, MMVF11, and C102/C104 fibrous glass blend, did not find exposure-related increases in lung tumor incidence (Goldstein et al. 1983; Haratake et al. 1995; Johnson and Wagner 1980; Kamstrup et al. 1998, 2001; McConnell et al. 1994, 1999; Muhle et al. 1987; Smith et al. 1987).

Intermediate-duration experiments did not provide evidence of carcinogenicity. No increased lung tumor incidence was found in female Wistar rats exposed nose-only to 252 fibers/cc (3 mg/m^3) of Code 104/475 special purpose glass fiber for 1 year (Muhle et al. 1987) or in small experiments (<16 animals/exposure group) with male Wistar rats exposed to 2.2 mg/m^3 of a glass wool (fiber counts not reported) for 1 year (Haratake et al. 1995), or rats, hamsters, and guinea pigs exposed to 70 fibers/cc of a ball-milled fiberglass (7% fiber) for 3 months (Lee et al. 1981b), with post-exposure periods up to 1 year.

In male Wistar rats exposed whole-body to 1,022 WHO fibers/cc of special purpose 104E-glass fiber for 1 year followed by a 1-year recovery period, the combined lung tumor incidence was statistically significantly different from controls (3/43 versus 1/38 adenomas and 7/42 versus 1/38 carcinomas, respectively) (Cullen et al. 2000); additionally, one mesothelioma was induced (1/43 versus 0/38 for controls). Exposure of rats to 1,119 WHO fibers/cc of special purpose glass fiber code 100/475 using the same protocol did not induce any mesotheliomas or statistically significantly increased incidences of lung tumors (Cullen et al. 2000).

One pleural mesothelioma (1/83 versus 0/83 for controls) and no lung tumors were observed in male Syrian Golden hamsters exposed to 310 WHO fibers/cc (37 mg/m^3) of MMVF33, a durable special applications glass fiber for 18 months (Hesterberg et al. 1999). No lung tumors or mesotheliomas were observed in male Syrian Golden hamsters exposed to 339 WHO fibers/cc (29.6 mg/m^3) of MMVF10a

glass wool (a low fluorine preparation of MMVF10) for 18 months (McConnell et al. 1999). No lung tumors and no increased incidences of bronchoalveolar metaplasia were seen in male Syrian Golden hamsters or female Osborne-Mendel rats exposed for 2 years to 300 or 3,000 fibers/cc of a 0.45 μm diameter glass wool (0.3 or 3.0 mg/m^3), 100 fibers/cc of a 3.1 μm diameter glass wool (10 mg/m^3), 10 or 100 fibers/cc of 5.4 μm diameter glass wool (1.2 or 12 mg/m^3), 25 fibers/cc of 6.1 μm diameter glass wool (9 mg/m^3), or 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/m^3) (Smith et al. 1987). Similarly, tumor incidence was not elevated in male Fischer 344 rats exposed nose-only to three concentrations of MMVF10 or MMVF11 glass wool for 2 years (Hesterberg et al. 1993c). MMVF10 was tested at 29, 145, and 232 WHO fibers/cc (3.1, 17.1, and 27.8 mg/m^3) and MMVF11 was tested at 41, 153, and 246 WHO fibers/cc (4.8, 15.8, and 28.3 mg/m^3).

No tumors were seen in biopsies collected at 8, 18, and 30 months (2/animals per time point) from a group of 10 male baboons (*Papio ursinus*) exposed to 1,122 NIOSH fibers (lengths >5 μm)/cc of a blend of C102 and C104 fibrous glass wools (7.54 mg/m^3; 5.80 mg/m^3 respirable) for 35 months (Goldstein et al. 1983). The study was inconclusive because of the small numbers used and the small amount of tissue available for analysis.

Slag Wool. The limited animal inhalation studies identified for slag wool did not provide any evidence of carcinogenicity.

No lung tumors and no increased incidences of bronchoalveolar metaplasia were seen in male Syrian Golden hamsters or female Osborne-Mendel rats exposed for 2 years to 200 fibers/cc of a 2.7 μm diameter slag wool (10 mg/m^3) (Smith et al. 1987).

In male Fischer 344 rats exposed nose-only for 24 months to 30, 131, or 213 WHO fibers/cc (3.1, 16.1, or 29.9 mg/m^3) of MMVF22, a blast-furnace slag wool, no significant increases were seen in the individual or combined incidences of pulmonary adenoma or pulmonary carcinoma (McConnell et al. 1994).

Rock Wool. The limited animal studies identified for rock wool did not provide any evidence of carcinogenicity.

No tumors were reported in Fischer rats exposed to 10 mg/m^3 of rock wool (fiber count not reported) for 50 weeks and allowed to recover for 4 months prior to sacrifice (Johnson and Wagner 1980).

In male Fischer 344 rats exposed nose-only for 24 months to 34, 150, or 243 WHO fiber/cc (3.1, 16.1, or 30.4 mg/m^3) of MMVF21, a traditional basalt-based rock (stone) wool, no significant increases were seen in the individual or combined incidences of pulmonary adenoma or pulmonary carcinoma (McConnell et al. 1994). Similarly, in male Fischer 344 rats exposed nose-only to 291 WHO fibers/cc (30.1 mg/m^3) of MMVF34/HT, a newly developed high-temperature rock wool, for 2 years (6 hours/day, 5 days/week), lung tumor incidence was not significantly increased (Kamstrup et al. 1998, 2001).

Continuous Filament Glass. No inhalation cancer studies in animals with continuous glass filaments were identified. Because these fibers are not normally respirable (ACGIH 2001; Lee et al. 1995), studies have been limited to injection and implantation (see Section 3.2.4, Other Routes of Exposure).

Other Fibers. No mesotheliomas or increased incidences of lung adenomas (1/121 versus 2/130 for controls or lung carcinomas (1/121 versus 0/130 for controls) were seen in male Fischer 344 rats exposed to 180 WHO fibers/cc (30 mg/m^3) of X-607 (Hesterberg et al. 1998b).

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to synthetic vitreous fibers.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculo-skeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals after oral exposure to synthetic vitreous fibers.

No studies were located regarding the following effects in humans or animals after oral exposure to synthetic vitreous fibers:

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to synthetic vitreous fibers.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to synthetic vitreous fibers.

Dermal Effects. Strong itching and contact dermatitis (with erythema, maculae, papules, and other eczematous symptoms) have been associated with occupational exposure to synthetic vitreous materials, including glass wool insulation and fiberglass fabrics (Bendsoe et al. 1987; Bjornberg 1985; Bjornberg et al. 1979a, 1979b, 1979c; Fisher 1982; Fisher and Warkentin 1969; Heisel and Hunt 1968; Koh and Khoo, 1995; Longely and Jones 1966; Minamoto et al. 2002; Possick et al. 1970; Stam-Westerveld et al. 1994; Tarvainen et al. 1993), rock wool (Bjornberg and Lowhagen 1977; Eun et al. 1991; Fisher 1982; Kiec-Swierczynska and Szymczk 1995; Peterson and Sabroe 1991; Thriene et al. 1996), and refractory ceramic fibers (Kiec-Swierczynska and Wojtczak 2000). The skin irritation has been associated with fibers

having diameters >5 μm and becomes less pronounced with continued exposure, a "hardening" of the skin (ACGIH 2001; Heisel and Hunt 1968; Stam-Westerveld et al. 1994).

No studies were located regarding the dermal effects of synthetic vitreous fibers in animals after dermal exposure.

Ocular Effects. Occupational exposure to fibrous glass materials, including glass wool insulation and fiberglass fabrics, has been associated with acute eye irritation (Longley and Jones 1966; Petersen and Sabroe 1991; Stokholm et al. 1982).

No studies were located regarding the ocular effects of synthetic vitreous fibers in animals after dermal exposure.

No studies were located regarding the following effects in humans or animals after dermal exposure to synthetic vitreous fibers:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

No studies were located regarding adverse health effects in humans after exposure by other routes to synthetic vitreous fibers.

Intratracheal instillation, interpleural implantation, and intraperitoneal injection studies with synthetic vitreous fibers have been performed. Most have been acute-duration studies (single administration followed by observation periods up to 2 years). The relevance of these studies to human inhalation exposure is unclear because of the high doses and rapid dose rates used, the bypassing of the natural

defense systems of the nasal and upper respiratory system, and the overloading or lack (for intraperitoneal studies) of pulmonary clearance mechanisms

Continuous Filament Glass Fibers. Neither intrapleural implantation (Stanton et al. 1972, 1977) nor intraperitoneal injection of continuous glass filaments into rats was carcinogenic (Pott et al. 1987).

Glass Wool. Studies in which glass wool was instilled into the trachea of animals were equivocal; some (but not all) demonstrated pulmonary fibrosis (Feron et al. 1985; Mohr et al. 1984; Pickrell et al. 1983; Renne et al. 1985; Smith et al. 1987; Wright and Kuschner 1977). Only two of these studies reported tumor induction in rats and hamsters (Mohr et al. 1984; Smith et al. 1987).

Rock Wool. Intratracheal instillation of rock wool did not cause tumor formation in female Syrian Golden hamsters (Adachi et al. 1991).

Slag Wool. No studies were located regarding the adverse health effects of slag wool in animals following other routes of exposure.

Refractory Ceramic Fibers. Intratracheal instillation of a refractory ceramic fiber caused lung cancer in male Syrian Golden hamsters, but not in female Osborne-Mendel rats (Smith et al. 1987). Intraperitoneal injection of ceramic aluminum silicate fibers in rats and hamsters induced cancer (Davis et al. 1984; Smith et al. 1987). Refractory alumina and zirconia fibers injected intraperitoneally did not induce fibrosis in rats (Pigott and Tshmael 1981).

3.3 GENOTOXICITY

No evidence for genotoxic activity of several synthetic vitreous fibers was found in bacterial mutation assays (Chamberlain and Tarmy 1977) or sister chromatid exchange assays in cultured human cells (Casey 1983). However, several cytogenetic effects have been observed in other *in vitro* assays. Notably absent are data on genotoxic end points following *in vivo* exposure of animal or humans to synthetic vitreous fibers. Results from short-term *in vitro* genotoxicity assays are of limited applicability to *in vivo* exposure scenarios because of evidence that long-term residence of synthetic vitreous fibers in the principal toxicity target, the lung, can lead to changes (dissolution, breakage into shorter fibers) that can decrease biological activities of longer fibers (IARC 2002; also see Section 3.4).

Synthetic vitreous fibers induced: chromosomal aberrations in cultured Chinese hamster cells (Brown et al. 1979a, 1979b); morphological transformations in Syrian hamster embryo cells (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Oshimura et al. 1984) and BALB/c-3T3 cells (Gao et al. 1995; Whong et al. 1999); micronuclei and multinuclei in Chinese hamster ovary cells (Hart et al. 1992), Chinese hamster lung fibroblasts (Ong et al. 1997; Zhong et al. 1997), Syrian hamster epithelial lung cells (Peraud and Riebe-Imre 1994), Syrian hamster embryo fibroblasts (Dopp and Schiffmann 1998), and human amniotic fluid cells (Dopp and Schiffmann 1998; Dopp et al. 1997); polyploidy in Chinese hamster lung cells (Koshi et al. 1991; Sincock et al. 1982); and deoxyribose nucleic acid (DNA) strand breaks and DNA-DNA interstrand crosslinks in human lung epithelial A549 cells (Wang et al. 1999b). In addition, several synthetic vitreous fiber types have been demonstrated to damage isolated DNA (Donaldson et al. 1995c) and to hydroxylate 2-deoxyguanosine to 8-hydroxydeoxyguanosine, presumably via hydroxyl radicals (Leanderson et al. 1988, 1989).

There is evidence that fiber dimensions can influence *in vitro* cytogenetic activities (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Ong et al. 1997) and that synthetic vitreous fibers are often less active than asbestos fibers (e.g., Donaldson et al. 1995c; Leanderson et al. 1988, 1989; Peraud and Rieve-Imre 1994; Wang et al. 1999b). For example, thin glass fibers (diameters 0.1–0.2 μm, lengths >10 μm) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8 μm) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to <1 μm diminished the transforming activity.

Gene amplification of several proto-oncogenes, *H-ras*, *K-ras*, *c-myc*, and *c-fos*, has been reported in several transformed BALB/C-3T3 cell lines that were induced by a glass fiber (AAA-10 microfiber) (Whong et al. 1999). Point mutations, detected by sequencing analysis of DNA from several of the transformed cell lines, were also found in the proto-oncogene *K-ras*, and in the *p53* tumor suppressor gene (Whong et al. 1999). Induction of *c-fos* and *c-jun* proto-oncogenes by crocidolite asbestos was demonstrated in cultured hamster tracheal epithelial cells and rat pleural mesothelial cells, but induction activities of a glass wool (MMVF10) and a refractory ceramic fiber (RCF1) were much less in this test system (Janssen et al. 1994a).

3.4 TOXICOKINETICS

3.4.1 Absorption

Absorption of synthetic vitreous fibers across the epithelial layers of the respiratory tract, the gastro-intestinal tract, and the skin is expected to be low to negligible due to the relatively large physical dimensions of these elongated particles (see Chapter 4). However, deposition of inhaled fibers on the surface of the epithelial layers of the respiratory tract is an initial process that has been well studied and, along with the process of lung clearance, plays an important role in determining toxicity (especially the deposition and clearance of fibers in the alveolar region of the respiratory tract). An overview of the deposition of inhaled synthetic vitreous fibers in the respiratory tract is presented in the next section (Section 3.4.1.1). The deposition of inhaled fibers has been reviewed in more detail in other published sources (Dai and Yu 1998; Jones 1993; Lippmann 1990; Morgan 1995; Oberdörster 1994, 2000; Stober 1972; Stober and McClellan 1997; Timbrell 1965; Yu et al. 1995a).

3.4.1.1 Inhalation Exposure

Very limited amounts of inhaled synthetic vitreous fibers are expected to be absorbed in humans or animals. Consistent with the expectation of limited, if any, absorption are findings from a study in which rats were given single intratracheally-instilled doses (1 mg/rat, equivalent to 3.5×10^6 fibers/rat) of a saline suspension of radiolabeled (^{24}Na) glass fibers (Morgan et al. 1993). The fibers were produced as a continuous filament with an approximate uniform diameter of 2 μm. The fibers in the instilled material had a log-normal distribution of lengths, with a median of 16 μm and geometric standard deviation of 1.8. Radioactivity measured in urine collected for 24 hours after dose administration accounted for <1% of administered radioactivity, and no radioactivity was detected in 24- to 48-hour urine samples. Radioactivity in feces collected for 48 hours and in the gastrointestinal tracts and lungs accounted for >96% of administered radioactivity in 4/8 rats sacrificed 48 hours after dose administration. The average total recovery of administered radioactivity in feces, gastrointestinal tract, and lungs of all eight rats was 93%. The average individual percentages of administered radioactivity in the feces, gastrointestinal tract, and lungs were 30, 2, and 61%. (In these experiments, radioactivity detected in the gastrointestinal tract and feces represents fibers deposited in the respiratory tract, removed by mucous flow to the gastro-intestinal tract, and eliminated with the feces—see Sections 3.4.2 and 3.4.4). Morgan et al. (1993) reported that, during dose administration, occasional losses of small volumes of the fiber suspension occurred (i.e., small volumes remained in the administration apparatus), and that these losses may account

for the small differences between the calculated administered doses of radioactivity and the total radioactivity recovered in the feces, gastrointestinal tract, and lungs.

There is evidence to suggest that a small amount of inhaled synthetic vitreous fibers may enter the body via the lymph nodes. For example, in hamsters exposed for 78 weeks to MMVF10a or MMVF33, elevated concentrations of fibers (# fibers/mg dry tissue) were measured in mediastinal tissue containing lymph nodes, the diaphragm, and the thoracic wall (Hesterberg et al. 1999).

The fraction of inhaled synthetic vitreous fibers deposited on the epithelial surface of the respiratory tract and the region where deposition occurs are determined by fiber dimensions, fiber density, ventilation parameters, and the structure and airway size of the respiratory tract (Dai and Yu 1998; Lippmann 1990; Morgan 1995; Yu et al. 1995a). In general, relatively thick inhaled fibers are deposited in the upper airways (i.e., the nasopharyngeal region and tracheobronchial regions), and only relatively thin fibers are carried to distal regions of the respiratory tract (i.e., the terminal bronchiole and alveolar regions). In the large conducting airway regions of the lung and in the nonciliated bronchoalveolar regions, fiber deposition is particularly enhanced at branching points (Brody and Roe 1983; Lippmann 1990; Myojo 1987).

In published studies of animals exposed by inhalation to different types of fibers, estimates of the fraction of inhaled fibers deposited in the lung have ranged from about 1–23% (Okabe et al. 1997). Given the complexity of factors influencing apparent lung deposition (e.g., fiber dimensions, exposure duration and concentration, ventilation parameters, and airways size and geometry) and the differences in experimental conditions and techniques used in these studies, the wide range is not surprising. However, studies that restricted periods of exposure to glass wool fibers to 30 minutes (Morgan 1995) or 10 minutes (Okabe et al. 1997) to minimize clearance by mucociliary action (see Section 3.4.2) reported values in the upper end of the range (15–23%).

Major mechanisms involved in the deposition of nonelectrostatically charged fibers in the respiratory tract include impaction (under high velocity airflows experienced in the larger airways of the respiratory tract), gravitational sedimentation (under low velocity airflows), interception, and diffusion. Impaction and sedimentation are influenced by the aerodynamic diameter of the particle, whereas interception is influenced by the length of the fiber. One formula for aerodynamic diameter (DA) of fibers is:

$$DA = 1.3\, p^{1/2} d^{5/6} L^{1/6}$$

where p=particle density; d=actual diameter; and L=length (Hesterberg and Hart 2001; Stober 1972). For glass fibers of uniform particle density, aerodynamic diameters are described by the following formula:

$$DA = 66d\left[\frac{\beta}{2+4\beta}\right]^{2.2}$$

where β=length:diameter ratio (Gross 1981). Calculated values of aerodynamic diameters of fibers of a uniform density range from about 2.5–4 times that of the actual diameter (Gross 1981; Timbrell 1965). More complicated mathematical expressions for aerodynamic diameters of fibers have been derived to account for changing orientation of fibers with respect to direction of airflow (Dai and Yu 1998). Fibers or particles with aerodynamic diameters >3–5 μm are expected to be predominantly deposited in the upper airways and have less probability of traveling to the lower lung than particles or fibers with smaller aerodynamic diameters (Morgan et al. 1980; Oberdörster 1994). Based on a review of the literature on particle deposition in the human lung, ACGIH (2001) published an algorithm predicting the collection efficiency of particles of varying aerodynamic diameters. The algorithm predicts that inhalation exposure to particles of uniform aerodynamic diameters of 1, 5, 6, or 10 μm would lead to the following mass percentages being deposited in the alveolar or gas-exchange region: 97, 30, 17, or 1%.

More specific mathematical models to predict the deposition of inhaled fibers in rodents and humans have been developed and are discussed in more detail by Yu et al. (1995a) and Dai and Yu (1998), and in Section 3.4.5, Physiologically Based Pharmacokinetic/Pharmacodynamic Models. The fraction of inhaled fibers that is deposited in the alveolar region is of particular toxicologic interest because fibers deposited in this region are more slowly removed than fibers deposited in the nasopharyngeal or tracheobronchial regions. Models that predict alveolar deposition fraction for refractory ceramic fibers in rats, hamsters, and humans have been used to examine the influence of differences in ventilation parameters, airway size, and fiber characteristics on this important parameter (Dai and Yu 1998). The human model predicts that increasing workload reduces alveolar deposition fraction and switching from nose-breathing to mouth-breathing increases alveolar deposition fraction. The models predict that alveolar deposition of fibers with aerodynamic fibers >3.5 μm and length:diameter ratios >10 is insignificant in rats and hamsters, whereas in humans, considerable alveolar deposition occurs with fibers having aerodynamic diameters as large as 5–6 μm. For example, for exposure to fibers with 30 μm length, 1.5 μm diameter, and 3.26 μm aerodynamic diameter at an air concentration of 1 fiber/cc, calculated alveolar deposition fractions

(expressed as percentage of inhaled fibers) were 0.04% for rats, 0.27% for hamsters, and 6.82% for humans (Dai and Yu 1998).

3.4.1.2 Oral Exposure

No studies were located examining the possible absorption of ingested synthetic vitreous fibers in humans or animals.

3.4.1.3 Dermal Exposure

No studies were located examining the possible absorption of synthetic vitreous fibers across the skin of humans or animals.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Fibers deposited on the epithelial surfaces of the nasal passages and the tracheobronchial tree, which are lined with ciliated cells and coated with a mucous layer, are quickly removed by the flow of mucous to the pharynx and swallowed into the gastrointestinal tract. This mechanical distribution is generally thought to be completed within about 24–48 hours (Jones 1993; Lippmann 1990; Morgan and Holmes 1980; Oberdörster 1994). A small fraction of fibers deposited in the trachea can be retained within the epithelium, as demonstrated in rats intratracheally instilled with suspensions of glass fibers (Morgan 1995; Morgan et al. 1994a).

The removal and clearance of fibers deposited on epithelial surfaces of the lower lung, which are lined with nonciliated cells without a mucous layer, is comparatively slow. Clearance from this region is accomplished by several mechanisms: engulfment by macrophages (phagocytosis) and movement to the mucociliary escalator (sometimes referred to as mechanical macrophage-mediated clearance); dissolution (either in near neutral [pH 7.4–7.5] extracellular pulmonary fluid or in presumably acidic [pH 4.5–5] phagolysosomes of macrophages); and translocation of fibers to the interstitium, the lymphatic circulation, and the pleural cavity. These mechanisms influence the biopersistence of inhaled fibers, which, along with deposited dose and fiber dimensions, play key roles in determining pulmonary

pathogenesis. Some data illustrating these distribution mechanisms are discussed in this section. For more comprehensive reviews, the reader is referred to recent papers by Bernstein et al. (2001a, 2001b), Hesterberg and Hart (2000, 2001), and Oberdörster (2000) and other earlier papers (Bellmann et al. 1994a, 1994b; Bernstein et al. 1995; Muhle and Bellmann 1995, 1997; Musselman et al. 1994; Oberdörster 1994).

Macrophages are motile cells found in the lung interstitium, on the surface of epithelial cells lining the alveoli, and on the surface of ciliated epithelial cells (Carpenter and Wilson 1999; Valberg and Blanchard 1991). They are capable of engulfing foreign materials in the conducting airways, the alveoli, and the interstitium and moving onto the mucociliary escalator. Macrophages facilitate a major clearance mechanism for the lower respiratory tract. Macrophage engulfment, however, is limited to fibers with lengths less than the diameter of the macrophage. Alveolar macrophage diameters range from about 10–13 μm in rats and 14–21 μm in humans (Hesterberg and Hart 2001; Oberdörster 2000). Fibers longer than about 20 μm are not expected to be cleared by macrophages unless they undergo transverse breakage (Eastes et al. 2000; Hesterberg and Hart 2001; Hesterberg et al. 1998a; Oberdörster 2000).

Results from early studies of lung clearance of intratracheally-instilled glass wool fibers of varying lengths in rats provided evidence of the inability of macrophages to engulf and clear long fibers, the dissolution and transverse breakage of synthetic vitreous fibers in the lung, and the limited degree to which fibers may be translocated to the lymph nodes (Morgan et al. 1982). In these studies, rats were given single intratracheal instillations of sized glass wool fibers with median diameters of about 1.5 μm and median lengths of 5, 10, 30, or 60 μm.

Long Fibers are Poorly Cleared by Macrophages. For the 5- and 10-μm length fibers, the number of fibers remaining in lungs declined smoothly with time after administration (Morgan et al. 1982). At 1 year, 90 and 80% of the injected 5- and 10-μm length fibers, respectively, had been cleared. In contrast, the number of fibers in lungs of rats exposed to 30- or 60-μm length fibers did not decline over a 9-month period after administration, indicating no discernible clearance. The fibers recovered at 9 and 18 months from the lungs of rats exposed to 60-μm length fibers showed evidence of transverse breakage of the fibers. The respective median lengths of recovered fibers at these times were 40 and 25 μm. The number of fibers in lungs at 9 months was 20–30% greater than the number in lungs of similarly exposed rats at 2 days after administration. (Fibers were not counted at 18 months because the 9-month results indicated

that transverse breakage would influence recovered fiber number more than any possible clearance mechanism).

Glass Fibers Dissolve at pH 7.4–7.5. Fibers recovered at 18 months also showed decreased diameters indicating dissolution within the lung (Morgan et al. 1982). Median diameters of recovered fibers at 18 months in the groups exposed to 5-, 10-, 30-, and 60-µm length fibers were decreased by 12, 28, >50, and >50%, respectively, of the original 1.5-µm diameters, indicating faster dissolution of longer fibers than shorter fibers. This result is consistent with the faster *in vitro* dissolution of glass fibers at pH 7.4–7.5 (the pH of extracellular fluid in the lung) than at acidic pHs (4.5–5) found within the phagolysosomes of macrophages (Oberdörster 2000). However, not all types of synthetic vitreous fibers show faster *in vitro* dissolution at pH 7.4–7.5 than at acidic pHs. For example, MMVF34, a stone wool, has been shown to be very biosoluble in the rat lung, poorly soluble *in vitro* at pH 7.4–7.5, and soluble *in vitro* at pH 4.5 (Hesterberg and Hart 2001).

Limited Translocation of Fibers to the Lymphatic Circulation may Occur. One year after administration, the fibers detected in hilar lymph nodes of rats exposed to 5-µm long glass fibers accounted for only 4% of the total lung fiber number (Morgan et al. 1982). The hilar lymph nodes contained smaller proportions of recovered fibers in rats exposed to the 10- and 30-µm length fibers. At the same time period, no fibers were detected in the hilar lymph nodes of rats exposed to 60-µm length fibers. The results indicate that only limited numbers of glass fibers were translocated to the lymph nodes under these experimental conditions.

Other studies with rats, hamsters, or guinea pigs indicate that considerable translocation of inhaled fibers to lymph nodes and the pleural cavity can occur under conditions that overload the mucociliary clearance mechanism (Lee et al. 1981a). In these studies, animals were exposed by inhalation to high concentrations (2,900, 13,500, or 41,800 fibers/cc) of potassium octatitanate fibers (average length of 6.7 µm and diameter of 0.2 µm) for 3 months. Numerous dust-laden macrophages were observed in tracheobronchial and mediastinal lymph nodes and in mediastinal adipose tissue adjacent to the lymph nodes when the animals were sacrificed 15 months after exposure ceased. Dust-laden macrophages also accumulated in the pleural cavity. Exposed animals showed fibrosis in the respiratory bronchiolar region and hyperplasia of the pleural mesothelium that increased in severity with exposure concentration (Lee et al. 1981a).

Evidence of rapid translocation of small numbers of short and thin fibers to pleural tissue has been observed in rats and hamsters after inhalation exposure to a refractory ceramic fiber, RCF1 (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996c, 1999). In an acute exposure study, rats were exposed (nose-only) to concentrations of 2,645 WHO respirable fibers/cc (length:diameter ≥3:1, length >5 μm, diameter <3 μm) 6 hours/day for 5 days (Gelzleichter et al. 1996a, 1996c). The aerosol concentration of total fibers (length:diameter ratio ≥3:1) was 6,206 fibers/cc. Rats were sacrificed immediately after and 32 days after exposure. Fiber concentrations and dimensions in lung and pleural tissue samples were measured using scanning electron microscopy. At both sampling dates, lung fiber concentrations were about 1,000-fold greater than pleural fiber concentrations, indicating that relatively small numbers of fibers were translocated from the lung to the pleura. Average pleural fiber concentrations declined from 25,000 fibers/pleura at day 5 to 15,700 fibers/pleura at day 32, indicating some clearance of pleural fibers after exposure ceased. All fibers found in pleural tissues had lengths <5 μm and diameters <0.35 μm. Fibers detected in the pleural samples had geometric mean lengths of 1.4 and 1.5 μm, and geometric mean diameters of 0.87 and 0.10 μm, at days 5 and 32, respectively. In contrast, geometric mean lengths and diameters of fibers detected in lung tissue were notably larger than pleural fibers and were similar to the values for the exposure aerosol (geometric mean length, 4.54 μm [range: 0.7–111 μm] and geometric mean diameter, 0.56 μm). In subsequent studies in which rats or hamsters were exposed to about 300 WHO fibers/cc of RCF1, 4 hours/day, 5 days/week for up to 12 weeks, fibers detected in pleural tissue (sampled at 4 or 12 weeks or 12 weeks after exposure ceased) also displayed shorter mean lengths and thinner mean diameters than the fibers in the exposure aerosol (Everitt et al. 1997; Gelzleichter et al. 1999). In lung tissues in both species at all time points, fibers longer than 5 μm accounted for approximately 67% of detected fibers, whereas in pleural tissue, fibers longer than 5 μm accounted for 12% in hamsters and 4% in rats (Gelzleichter et al. 1999).

The biopersistence of fibers in lungs has been examined in several studies of rodents following acute (5-day) inhalation exposures to a number of glass wools, continuous filament glass, rock and slag wools, and a refractory ceramic fiber, as well as amosite or crocidolite asbestos (Bernstein et al. 1996; Eastes and Hadley 1995; Hesterberg et al. 1996, 1998a, 1998b). Lung tissues were sampled at several times after exposure from 1 hour up to 1 year, and concentrations and dimensions of fibers in the tissues were measured using scanning electron microscopy. These studies focused on the clearance of fibers with lengths >20 μm, which is thought to be mediated mainly by dissolution and subsequent transverse breakage, rather than direct mechanical macrophage-mediated clearance. One- and two-compartment first-order exponential models were fit to lung concentration data for fibers with lengths >20 μm. For

most fiber types, the two-compartment model provided a better fit than the one-compartment model. From the two models, two measures of lung clearance were used to compare the biopersistence of fiber types—a weighted clearance half-time that incorporated the half-times from the slow and fast compartment of the two-compartment model ($WT_{1/2}$: Bernstein et al. 1996) or the days required for clearance of 90% of the fibers with lengths >20 μm that were present in the lung 1 day after cessation of exposure. For fiber types for which a two-compartment model did not provide an improved fit over a one-compartment model, clearance half-time ($T_{1/2}$) was compared with $WT_{1/2}$ for the other fibers.

Using either measure of lung biopersistence ($WT_{1/2}$ or T-90 for fibers with lengths >20), synthetic vitreous fibers showed a considerable range of values, but all were markedly less biopersistent than amosite and crocidolite asbestos (Table 3-2). Amosite and crocidolite asbestos showed high $WT_{1/2}$ values (418 and 817 days, respectively), several durable synthetic vitreous fibers showed moderately high $WT_{1/2}$ values between 37 and 91 days, and several glass wools, a slag wool, and newly developed rock wools showed $WT_{1/2}$ values below 13 days (Table 3-2).

The dissolution of a variety of synthetic vitreous fibers has been extensively studied *in vitro* in simulated physiological fluids (Bernstein et al. 1996; Christensen et al. 1994; Eastes and Hadley 1995; Knudsen et al. 1996; Mattson 1994; Potter and Mattson 1991; Scholze and Conradt 1987). These studies are often conducted at pH 7.4 to simulate acellular dissolution and pH 4.5 to simulate dissolution in the acidic phagolysosomes of macrophages. The following equation is fit to *in vitro* data for changing fiber diameter (D) with time (t) to provide estimates of K_{dis}, the dissolution rate coefficient, for different fiber types:

$$D(t) = D_0 - 2K_{dis}t / \rho$$

where ρ is the density of the fiber, and K_{dis} is usually in units of ng/cm^2-hour. A larger coefficient indicates faster dissolution. Amphibole asbestos fibers, such as crocidolite or amosite, essentially do not dissolve at pH 7.4 and have K_{dis} values <1 (Table 3-2). In contrast, synthetic vitreous fibers dissolve, but show variance among fiber types in rates of dissolution. K_{dis} values for synthetic vitreous fibers in Table 3-2 range from 3 to >500 ng/cm^2-hour. *In vitro* dissolution rates are correlated with rates of lung clearance, but several exceptions indicate that dissolution at pH 7.4 is not the only determinant of lung biopersistence (Table 3-2). For example, MMVF34 (HT rock wool) has a moderately low *in vitro* pH 7.4 K_{dis} (59 ng/cm^2-hour), but displays very fast lung clearance ($WT_{1/2}$=6 days). In contrast, MMVF10 (insulation glass wool) has a high pH 7.4 K_{dis} (300 ng/cm^2-hour), but displays slow lung clearance

Table 3-2. Lung Clearance of Fibers with Lengths >20 µm in F344 Male Rats Following Nose-only Inhalation Exposure (6 Hours/Day for 5 Days) to 19 Different Synthetic Vitreous Fibers or Two Types of Asbestos

Fiber name	Type	Weighted half-time ($WT_{1/2}$, days)	90% clearance (T-90, days)	*In vitro* K_{dis}, pH 7.4[a]
Amosite	Asbestos	418	2,095	<1
Crocidolite	Asbestos	817[b]	2,270	<1
MMVF32	Special application continuous filament glass	79	371	9
MMVF21	Rock (stone) wool	67 (91)[c]	264 (206)[c]	21
RCF1a	Refractory ceramic fiber	55	227	3
MMVF33	Durable special applications glass	49	240	12
L	Traditional rock wool	45	186	20
MMVF10	Insulation glass wool	37[b]	123	300
H	New rock wool	13	49	270
MMVF11	Insulation glass wool	9 (13)[c]	38 (40)[c]	100
MMVF22	Slag wool	9	37	400
J	Experimental	10	18	170
F	New rock wool	9[b]	28	160
MMVF34	New rock wool (HT fiber, soluble in acid)	6	19	59
O	Rock wool	6[b]	20	>500
P	Glass wool	6[b]	19	>500
M	Glass wool	5[b]	18	>500
G	New rock wool	5[b]	18	210
A	New glass wool	4	9	250
C	New glass wool	4	14	>500
B	B-01/09 (glass wool)	2	8	>500

[a]K_{dis} is the empirically derived coefficient (in ng/cm^2-hour) for *in vitro* dissolution in a flowing physiological saline solution at pH 7.4. A larger coefficient indicates faster dissolution.
[b]Values are half-times ($T_{1/2}$) from a one-compartment model; the two-compartment model did not provide an improved fit.
[c]Values in parentheses are from a second experiment.

Source: Hesterberg et al. 1998a

($WT_{1/2}$=37 days) compared with other synthetic vitreous fibers. Short-term *in vivo* lung clearance tests and *in vitro* dissolution tests have been proposed as preliminary screening tools to predict lung biopersistence and subsequent toxicity of untested fibers (Davis et al. 1996; Eastes et al. 2000; Zoitos et al. 1997).

Results from short-term *in vivo* lung clearance tests reflect the accumulation and biopersistence of fibers in the lungs of animals exposed for chronic durations. For example, lung elimination half-times for fibers with lengths >20 μm after 5 days of inhalation exposure of rats to comparable concentrations of rock wools MMVF21 or MMVF 34 (HT rock wool) were 92 days and 5 days, respectively, reflecting moderate and low biopersistence of the two rock wools (Kamstrup et al. 1998). This difference in biopersistence was reflected in lung concentrations in rats exposed (nose-only, 6 hours/day, 5 days/week) to comparable concentrations of the two rock wools for up to 18 months. Rats exposed to MMVF34 showed lung concentrations for fibers with lengths >20 μm of 8, 11, 10, and 11 fibers per mg dry lung $x10^3$ at respective sampling times of 3, 6, 12, and 18 months. These findings are consistent with early attainment of a balance between continued exposure and fast dissolution (i.e., low biopersistence) of this fiber. In contrast, concentrations in rats exposed to the moderately biopersistent fiber, MMVF21, were higher and showed evidence of accumulation with time at the same sampling times: 18, 23, 55, and 62 fibers per mg lung $x10^3$.

3.4.2.2 Oral Exposure

No studies were located examining distribution of ingested synthetic vitreous fibers in humans or animals.

3.4.2.3 Dermal Exposure

No studies were located examining distribution of dermally applied synthetic vitreous fibers in humans or animals.

3.4.2.4 Other Routes of Exposure

The clearance kinetics of a variety of synthetic vitreous fibers from the respiratory tract following intratracheal instillations of suspensions of fibers has been studied in several animal species including

rats, hamsters, and sheep (Bellmann et al. 1994a, 1994b, 1995; Dufresne et al. 1999; Eastes et al. 1995; Morgan et al. 1982, 1994a; Morris et al. 1995; Searl et al. 1999). Intratracheal instillation offers the advantage of being less expensive than inhalation experiments, and results from these studies are supportive of results from clearance studies following inhalation. For example, the intratracheal instillation study by Morgan et al. (1982) discussed in the previous section provided evidence of the inability of macrophages to engulf and clear long fibers, the dissolution and transverse breakage of synthetic vitreous fibers in the lung, and the limited degree to which fibers may be translocated to the lymph nodes. However, this mode of administration has a few disadvantages, relative to inhalation exposure, including the increased potential to form clumps of fibers and the induction of inflammatory responses to high bolus doses (Oberdörster 2000). Because clumping and inflammation may influence fiber dissolution and clearance, the results from clearance studies following intratracheal instillations are not discussed further in this section.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Synthetic vitreous fibers are not metabolized via typical enzyme-mediated processes, but undergo dissolution at varying rates depending on fiber composition, manufacturing processes under which the fibers were formed, and physical and chemical conditions in which the fiber may exist (Hesterberg and Hart 2001; Zoitos et al. 1997). In general, the dissolution of vitreous fibers in physiological fluids is thought to occur via reactions in which a water molecule (or some part thereof) replaces a cation in the matrix of the fiber (Eastes et al. 2000). In the simplest model for dissolution, all components in the matrix are assumed to dissolve at approximately the same rate. This model is used in the traditional determinations of K_{dis}, the *in vitro* dissolution rate coefficient, for various fibers. However, for many synthetic vitreous fibers, certain components dissolve more rapidly than others. Vitreous fibers with high alumina and silica contents favor a uniform rate of dissolution of all components, whereas fibers with a lower proportion of alumina and silica (<63 mole%) show nonuniform dissolution rates in which oxides of calcium, magnesium, and potassium dissolve quickly, leaving a weakened silica matrix (Hesterberg and Hart 2001). At points where the matrix is weakened, applied physical stress can lead to transverse breakage of the fiber. More complicated models to predict fiber dissolution without assuming uniform dissolution rates for all components are under development (Eastes et al. 2000; Hesterberg and Hart 2001).

Synthetic vitreous fibers have amorphous molecular structures that do not have planes of cleavage such as those in the crystal structure of chrysotile asbestos. The longitudinal cleavage of asbestos fibers can form thinner fibers that may more readily move into the interstitium or the pleura cavity (Agency for Toxic Substances and Disease Registry 2001). This property is not expected with synthetic vitreous fibers and may contribute to the difference in potency between asbestos and synthetic vitreous fibers. In addition, asbestos fibers, especially amphibole fibers, undergo very little, if any, dissolution in *in vitro* pH 7.4 tests (see Table 3-2). The relatively high persistence of long amphibole asbestos fibers in lungs is demonstrated by long clearance half-times of amphibole asbestos in rats (as shown in Table 3-2). Chrysotile asbestos, the least persistent asbestos type, is also expected to be more persistent in lungs than most synthetic vitreous fibers. For example, in rats following 10-day inhalation exposure to similar concentrations of chrysotile or a special purpose Code 100/475 glass fiber, the lung clearance half-time for long (>15 μm) chrysotile fibers was 46.2 weeks, whereas the half-time for long Code 100/475 glass fibers was 6.6 weeks (Searl 1997).

3.4.3.2 Oral Exposure

No studies were located regarding compositional or structural changes in synthetic vitreous fibers in the gastrointestinal tract.

3.4.3.3 Dermal Exposure

No studies were located regarding compositional or structural changes in synthetic vitreous fiber after dermal exposure.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

As discussed in Section 3.4.2.1, the principal pathways by which synthetic vitreous fibers are removed from the respiratory tract involve (1) mechanical mucociliary translocation to the pharynx, swallowing into the gastrointestinal tract, and elimination in the feces, (2) dissolution, and (3) transverse breakage of long fibers into shorter fibers. Mechanical translocation is mediated directly with fibers deposited on the surface of the ciliated epithelium of the respiratory tract and via macrophages when fibers are deposited in

the nonciliated epithelial region in the lower respiratory tract. After fibers or fiber-laden macrophages are on the mucociliary escalator, mechanical translocation is thought to be complete within about 24–48 hours (Jones 1993; Lippmann 1990; Morgan and Holmes 1980; Oberdörster 1994). Clearance of synthetic vitreous fibers from the lower airways is slower but shows variance with fiber types and dimensions. For example, clearance half-times for fibers longer than 20 μm in the lungs of rats have been reported to range from 2 to 79 days for 19 different synthetic vitreous fibers (Hesterberg et al. 1998a; see Table 3-2). For asbestos fibers in rats, more rapid clearance of shorter (<5 μm) fibers than of longer (>10 or 20 μm) fibers has been observed. This is explained as a result of the relative difficulty with which longer fibers are engulfed by macrophages. In contrast, many synthetic vitreous fibers show a more rapid clearance rate for long fibers compared with short fibers. This difference is consistent with the inability of macrophages to engulf long fibers, the relatively rapid dissolution of many synthetic vitreous fibers in the near-neutral pH solution of the intracellular spaces in the lung, and the subsequent transverse breakage of long vitreous fibers into shorter fibers. For example, lung clearance half-times in rats for long (>20 μm) fibers were 44, 6, and 986 days for MMVF10, MMVF11, and crodidolite asbestos, respectively; for short (<5 μm) fibers, the respective half-times were 111, 46, and 44 days (Hesterberg et al. 1996).

3.4.4.2 Oral Exposure

No studies were located regarding excretion of synthetic vitreous fibers after oral exposure. Most, if not all, synthetic vitreous fibers that are ingested are expected to be excreted in the feces. Fecal elimination of a single oral dose of asbestos fibers has been demonstrated to be essentially complete within 48 hours (Gross and Stanton 1974).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of synthetic vitreous fibers following dermal exposure, but it is generally considered that dermal exposure does not result in absorption of these fibers.

3.4.4.4 Other Routes of Exposure

As with inhaled fibers, intratracheally-instilled synthetic vitreous fibers are cleared by mucociliary translocation, dissolution, and transverse breakage (Bellmann et al. 1994a, 1994b, 1995; Dufresne et al. 1999; Eastes et al. 1995; Morgan et al. 1982, 1994a; Morris et al. 1995; Searl et al. 1999). Fibers swallowed into the gastrointestinal are efficiently excreted in the feces.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The

numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species.

PBPK models for insoluble or slowly soluble inhaled materials, such as synthetic vitreous fibers, focus on the retention of the inhaled materials in the alveolar region of the lung (Stober and McClellan 1997). The models recognize that alveolar retention (the net result of the deposition and clearance processes in the alveolar region) is also dependent on deposition and clearance of particles in the upstream regions of the respiratory tract. The models divide the respiratory system into a number of connected compartments (most often into the nasopharyngeal, tracheobronchial, and alveolar regions) with each compartment having a distinct set of deposition and clearance parameters. As reviewed below, alveolar retention models for refractory ceramic fibers have been developed for rats, hamsters, and humans; the rat model has recently been extended to other synthetic vitreous fibers such as glass, rock, and slag wools (Yu et al. 1994, 1995b, 1996, 1998a, 1998b).

Models for alveolar retention of refractory ceramic fibers in rats and hamsters have been developed based on: (1) theoretical and empirical understanding of deposition processes (e.g., sedimentation and impaction) in various regions of the respiratory tract as they are influenced by particle dimensions, airflow characteristics, and airway geometry; (2) understanding that clearance processes include direct

mechanical mucociliary clearance, macrophage-mediated mucociliary clearance, dissolution, and transverse breakage of long fibers into shorter fibers; and (3) data for lung concentrations and size distributions of fibers in animals exposed chronically to accurately measured inhaled concentrations of refractory ceramic fiber (RCF1) aerosols (Yu et al. 1994, 1995b, 1996). The rat model for refractory ceramic fibers was also extended to a more general model to apply to other synthetic vitreous fiber including glass wools and rock wools (Yu et al. 1998a, 1998b).

The most recent of the retention models developed by Yu and colleagues include mathematical descriptions of alveolar deposition rates with the following explanatory variables: tidal volume, breathing frequency, air concentrations of fibers of specific lengths and diameters, and alveolar deposition fraction of fibers with specific diameter and length. The deposition models account for the dependence of the fraction of inhaled fibers depositing in the alveolar region not only on the deposition efficiency of the alveolar region itself (i.e., the amount deposited divided by the amount entered), but also on deposition efficiencies in the nasopharyngeal and tracheobronchial regions. The clearance models describe removal of fibers from lungs by three simultaneous processes: alveolar macrophage-mediated clearance (as a function of fiber length and alveolar macrophage volume); dissolution (decrease in fiber diameter with time at a constant rate); and transverse breakage of long fibers into shorter fibers (Yu et al. 1996, 1997, 1998a, 1998b). Macrophage-mediated clearance in the model is also a function of lung burden, the total accumulated fiber and particle volume in the lung; the rate of clearance slows at high lung burdens.

Model simulations of lung concentrations of fibers of various length classes (lengths <5, 5–10, 10–20, and >20 μm) showed good agreement with empirical lung concentrations in rats exposed (nose-only, 6 hours/day, 5 days/week) for up to 104 weeks to RCF1 concentrations of 36, 91, 162, and 234 total fibers/cc (Yu et al. 1996). Good agreement was also found between model simulations and empirical lung concentrations in rats at various postexposure periods following exposure (nose-only, 6 hours/day for 5 days) to each of four types of synthetic vitreous fibers (two glass wools—MMVF10, MMVF11; one rock wool—MMVF21; or one slag wool—MMVF22) at gravimetric concentrations of 30 mg/m^3 (Yu et al. 1998a). Model simulations were also compared with lung concentration data for rats exposed by inhalation for up to 104 weeks to several concentrations of the same synthetic vitreous fibers (MMVF10, MMVF11, MMVF21, or MMVF22) (Yu et al. 1998b). The model simulations were reported to “compare quite well” with the data, but a statistical analysis of fit was not conducted.

A deposition and clearance model for refractory ceramic fibers in humans was developed from the rat model based on anatomical and physiological differences between rats and humans (Yu et al. 1995a, 1997). Some of the differences used in developing the human model are described in Table 3-3. Appropriate data to examine the accuracy of the human model are not available (i.e., lung fiber concentrations from autopsied lungs of exposed subjects and accurate information regarding time-weighted average air concentrations to which the subjects were exposed and durations of exposure). The model was used, however, to predict human lung concentrations following 15–20 years of occupational exposure to various air concentrations of refractory ceramic fibers. These were compared with lung concentration data for three workers who worked in a refractory ceramic fiber manufacturing plant for 13–17 years (Yu et al. 1997). The comparison suggested that one subject may have been exposed to an average air concentration of 0.25 fibers/cc and that the other subjects may have been exposed to 0.6–0.7 fibers/cc. These concentrations are within the range of air concentrations measured for some refractory ceramic fiber manufacturing plants (Yu et al. 1997).

For refractory ceramic fiber size ranges and concentrations encountered in workplaces, the deposition models predicted that: (1) the average alveolar deposition fraction in humans is 8.4% for nose-breathing and 15.9% for mouth-breathing; (2) the average alveolar deposition fraction in rats and hamsters are 3.7 and 5.7%, respectively; (3) humans have 1–2.5 times less deposited fiber per unit lung surface area than rats and hamsters; and (4) the geometric mean size dimensions (diameter and length) of fibers deposited in the lungs of rats and hamsters are smaller than those of fibers deposited in human lungs (Yu et al. 1995a).

One impetus to develop rat, hamster, and human alveolar retention models for synthetic vitreous fibers is to use the models to facilitate animal-to-human extrapolations of dose-response relationships for adverse effects in rodents exposed by inhalation to synthetic vitreous fibers (see Section 3.5.3, Animal-to-Human Extrapolations and Appendix A). Several quantitative human cancer risk estimates have been prepared using the data from the RCF1 2-year rat bioassay and the lung deposition and clearance models developed by C.P. Yu and colleagues (Maxim et al. 2003b; Moolgavkar et al. 1999, 2000; Turim and Brown 2003; Yu and Oberdörster 2000).

Table 3-3. Comparative Human and Rat Anatomical and Physiological Parameters Relevant to Alveolar Retention of Refractory Ceramic Fibers

Parameter	Human	Rat
Body weight (kg)	70	0.3
Lung weight (g)	1,000	1.48
Airway volume (cm^3)	3,200	6.5
Airway surface area (cm^2)	627,000	5,500
Number of alveolar macrophages	$7x10^9$	$2.6x10^7$
Alveolar macrophage volume (μm^3 per lung)	2,500	1,000
Total alveolar macrophage volume (mm^3)	17,500	26
Tidal volume (cm^3)	500	2.74
Breathing frequency ($minute^{-1}$)	14	98
Minute ventilation (cm^3/minute)	7,000	268
Life span (years)	70	2

Source: Yu et al. 1997

3.5 MECHANISMS OF ACTION

The mechanisms by which inhaled fibers and particles, including synthetic vitreous fibers, induce adverse effects on the lung and pleural membrane are incompletely understood, but extensive research over the past few decades with asbestos fibers, silica, and synthetic vitreous fibers of various types has led to a complex working hypothesis that includes pharmacokinetic mechanisms influencing the dose of fibers to the lung and toxicity mechanisms involving the responses of lung cells and tissues to retained fibers. Evidence has accumulated that these mechanisms are influenced to varying degrees by fiber dimensions, dose to the lung, and fiber durability; surface area and chemical composition not related to durability may also play roles in the mechanisms. This section provides a brief overview of mechanisms involved in fiber-induced effects on the lung (inflammation, cytotoxicity, genotoxicity, cell proliferation, fibrosis, and lung tumors) and the pleural membrane (pleural plaques, pleural thickening and pleural mesothelioma). More detailed and comprehensive information on this area of research can be found in reviews by Churg et al. (2000), Driscoll (1996), Hart et al. (1994), Hesterberg and Hart (2001), Hesterberg et al. (1993c), Kane (1996), and Mossman and Churg (1998).

3.5.1 Pharmacokinetic Mechanisms

The amount of fibers deposited in the alveolar region of the lung is a key determinant of the potential development of adverse effects in the interstitium of the lung and in the pleural membrane. The aerodynamic diameter of fibers, along with ventilation parameters and geometry and size of airways, strongly influence alveolar deposition (Dai and Yu 1998; Oberdörster 2000). Fibers with aerodynamic diameters >3–4 μm are mostly excluded from the alveolar region due to deposition in upstream regions of the respiratory tract. The fraction of inhaled fibers deposited in alveoli decreases to zero with aerodynamic diameters of about 5 μm in rats and 10 μm in humans (Dai and Yu 1998).

The mechanisms whereby fibers deposited in the alveoli move to the interstitium, the pleural membrane, or the lymphatic system are unknown, although it is believed that movement into these regions is enhanced when rates of dissolution and macrophage-mediated clearance are overwhelmed by intakes at high exposure concentrations (Gross and Stanton 1973; Oberdörster 2000). Using electron microscopy, recent experiments have detected predominately short (<5 μm) and thin (<0.35 μm) fibers in pleural tissues after acute or intermediate inhalation exposure of rats and hamsters to a refractory ceramic fiber,

RCF1 (Everitt et al. 1997; Gelzleichter et al. 1996a, 1996b, 1999). These findings suggest that rapid fiber movement into pleural tissues occurs and has size limitations. Whether the movement is principally passive through intracellular spaces or mediated by the movement of inflammatory cells is unknown. The detection of fibers in the pleural tissues in the intermediate-duration studies was accompanied by inflammation and cell proliferative changes in pleural tissue. Hamsters showed more severe pleural changes than rats, but this was not correlated with a greater total number of fibers in hamster pleural tissues (Everitt et al. 1997). However, more extensive subsequent examinations of fiber size distributions in pleural tissues from rats and hamsters following intermediate-duration exposure to RCF1 found that fibers longer than 5 μm accounted for 12 and 4% of the fiber burden in hamsters and rats, respectively (Gelzleichter et al. 1999). The pleural surface density of these "long" fibers in hamsters (150 fibers per cm^2) was about 2–3 times that in the rat, whereas the pleural burden of short (<5 μm) fibers in the rats was about 1.5–2 times that in the hamster. The differences between hamsters and rats in intermediate-duration pleural cell proliferative changes may be due, in part, to the differences in retained "long" fiber surface density, but contributions from other mechanisms, such as release of reactive oxygen species, cytokines, or growth factors from alveolar macrophages or other cells are also plausible (Adamson et al. 1994).

The dose of fibers that remains in the lower lung is a net result of the amount of fibers deposited and the amount of deposited fibers removed by macrophage-mediated clearance via the mucociliary escalator, and by the combined actions of dissolution and transverse breakage of long fibers into shorter fibers. Whereas fiber aerodynamic diameter is a critical factor for deposition, fiber length is a critical factor for macrophage engulfment. Fibers longer than 15–20 μm are expected to be too long for human macrophages to completely engulf and transport out of the lung. Thus, clearance of long fibers from the lower lung cannot occur until the fibers either dissolve or break into shorter fibers that can be removed by macrophages (Eastes et al. 2000; Hesterberg and Hart 2001; Hesterberg 1998a; Oberdörster 2000).

Dissolution of fibers is influenced by their chemical composition and structure. As discussed in Section 3.4, synthetic vitreous fibers of various types show a range of *in vitro* dissolution rates (that are correlated with *in vivo* lung clearance half-times in rats), but all synthetic vitreous fibers tested to date are less biopersistent than amphibole asbestos fibers, which undergo no dissolution and are very biopersistent. Vitreous fibers with relatively high alumina and silica contents favor a relatively uniform, slower rate of dissolution, but increasing content of oxides of calcium, magnesium, and potassium can

lead to nonuniform rates of dissolution, faster breakage, and faster clearance (Eastes et al. 2000; Hesterberg and Hart 2001; Morgan et al. 1994b; Potter and Mattson 1991).

When rates of fiber deposition exceed the rates of removal, fibers can accumulate in the lung leading to chronic and persistent inflammation and tissue damage. For a variety of synthetic vitreous fibers and some amphibole asbestos fibers (amosite and crocidolite) correlations have been demonstrated among fiber durability in simulated pH 7.4 physiological fluids, fiber breakage rates, fiber lung clearance half-times in rodent models, and the ability to induce prefibrotic lesions (e.g., cell proliferation or collagen deposition), fibrosis, or tumors in rodents following repeated inhalation exposure (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a). These correlations stress the importance of fiber durability in determining fiber pathogenicity and are the basis of proposals for using *in vitro* dissolution tests and short-term rodent lung clearance tests as preliminary screening tools to assess the potential toxicity of newly developed fibers. Measurements of *in vitro* dissolution rates for a number of synthetic vitreous fibers of varying chemical content indicate that substitution of sodium, potassium, boron, calcium, and magnesium in the silicate network tends to increase dissolution rate, whereas increasing aluminum oxide content tends to decrease dissolution rate.

In support of the hypothesis that chemical composition, fiber durability, and fiber pathogenicity are linked, Wardenbach et al. (2000) demonstrated a significant correlation between the potencies of seven synthetic vitreous fibers to induce tumors in rats following intraperitoneal injection and their "carcinogenicity index", which was defined as the summation of sodium-, potassium-, boron-, calcium-, magnesium-, and barium-oxide weight percentage minus 2 times the aluminum-oxide weight percentage. However, chemical composition is not expected to be the sole determinant of fiber biopersistence, as conditions in the manufacturing process, such as flame attenuation versus air attenuation, have been demonstrated to influence the dissolution rate of synthetic vitreous fibers (see Hesterberg and Hart 2001 for review).

3.5.2 Mechanisms of Toxicity

The deposition of relatively insoluble particles, such as synthetic vitreous fibers, in the lower lung of animals is well known to cause a complex defensive inflammatory response characterized by increased numbers of alveolar macrophages and other inflammatory cells. Chronic and persistent inflammation from deposited fibers (expected with continued high level exposure to all synthetic vitreous fibers) has

been linked for the most biopersistent synthetic vitreous fibers and asbestos to the development of cell injury, DNA changes, cell proliferation, deposition of collagen and other extracellular components leading to fibrosis (tissue scarring), and tumor development (Greim et al. 2001; IARC Expert Panel 1996; Kane 1996; Mossman and Churg 1998). Cellular and molecular events in these fiber-induced nonneoplastic and neoplastic effects are poorly understood, but several mechanistic hypothesis have been proposed based predominately on research with asbestos. The following discussion highlights results relevant to synthetic vitreous fibers.

The penetration or engulfment of fibers into macrophages, other inflammatory cells, epithelial cells, or mesothelial cells generates reactive oxygen and nitrogen species that can damage DNA, lipids, and proteins, lead to cytotoxicity, and stimulate release of inflammatory mediators, cytokines, and growth factors that may induce epithelial and mesothelial cell proliferation (Churg et al. 2000; Driscoll 1996; IARC Expert Panel 1996). Reactive oxygen species may also be generated by reactions on the surfaces of fibers, but this activity appears to be much greater with certain asbestos fibers (e.g., amosite) than with insulation wools (e.g., MMVF10) and refractory ceramic (e.g., RCF1) fibers (Gilmour et al. 1995, 1997). Experiments with cultured cells exposed to asbestos fibers have demonstrated that anti-oxidant systems can protect against fiber-induced cytotoxicity, providing support for the importance of reactive oxygen species in the development of fiber-induced disease (Mossman and Churg 1998).

Fibers of similar size distributions, but different chemical compositions, may elicit different responses from macrophages. For example, *in vitro* incubation of MMVF10 fibers with rat alveolar or peritoneal macrophages did not produce detectably increased levels of superoxide anions, but MMVF21 fibers with a similar distribution of fiber sizes caused increased production of superoxide anions by either type of macrophage (Dörger et al. 2001). This difference was associated with the finding that significantly higher numbers of macrophages completely phagocytized MMVF21 compared with MMVF10 fibers. The chemical or cellular basis for these differences is unknown, but may be related to lesser ability of MMVF10 fibers to directly elicit cytokines and proinflammatory mediators that modulate phagocytic functions of cells (Driscoll 1996).

In addition to fiber-induced reactive oxygen-mediated mechanisms that may lead to cytotoxic and cytoproliferative or hyperplastic responses, other proposed mechanisms in which fibers may directly induce cell proliferation include: (1) a “healing” response secondary to direct fiber-induced cell injury; (2) direct induction by fibers (at noncytoxic levels) of inflammatory cells and other lung cells to release

mediators that cause tissue damage and stimulate cell proliferation; and (3) a direct cell proliferative effect of fibers on cells (Driscoll 1996). It is likely that multiple mechanisms play variable roles in the cell proliferation responses to different fiber types and exposure scenarios. Understanding of the interactions among the possible multiple mechanisms is too incomplete to provide reliable in depth explanations for observed differences in apparent potency among fiber types, although there is sufficient evidence to indicate that fiber durability plays a key role. The comparative examination of cellular and molecular responses related to cell proliferation and inflammation from fibers with similar size distributions, but varying pathogenic potency, is an area of intensive current research (e.g., Barchowsky et al. 1997; Brown et al. 1998, 1999, 2000; Donaldson et al. 1995a, 1995b; Dörger et al. 2000, 2001; Gilmour et al. 1997; Jensen and Watson 1999; Johnson and Jaramillo 1997; Leikauf et al. 1995; Luoto et al. 1997; Marks-Konczalik et al. 1998; Morimoto et al. 1999a; Tsuda et al. 1999).

Fiber-induced cell proliferative responses that can lead to tissue scarring in the lung and pleural tissues are also thought to play a role in the development of lung carcinomas or mesotheliomas by enhancing the frequency of cells transformed by spontaneous or fiber-induced genetic changes (Driscoll 1997; Greim et al. 2001; IARC Expert Panel 1996; Kane 1996). Thus, the carcinogenic responses to synthetic vitreous fibers observed in animals may develop via both genotoxic and non-genotoxic modes of action. As discussed in Section 3.3, results from *in vitro* tests indicate that, like asbestos fibers, several types of synthetic vitreous fibers can induce cytogenetic changes and alter DNA. Proposed mechanisms for fiber-induced genetic changes include DNA alterations from reactive oxygen species and physical interference of fibers with cellular cytoskeletons and chromosomes (Kane 1996).

3.5.3 Animal-to-Human Extrapolations

As discussed in Section 3.4.5, there are distinct differences between animal species and humans in respiratory tract size and geometry, ventilation rates and patterns, and macrophage size that influence the retention (the net result of deposition and clearance) of fibers in the lung. Yu and colleagues have developed lung retention models for refractory ceramic fibers in rats, hamsters, and humans that incorporate many of these interspecies differences, some of which are shown in Table 3-3 (Dai and Yu 1998; Yu et al. 1994, 1995a, 1995b, 1996, 1997). The models incorporate mechanisms of deposition in the nasopharyngeal, tracheobronchial, and alveolar regions, macrophage-mediated clearance (with shorter fibers preferred and impaired clearance occurring at high levels of fiber lung concentration), fiber dissolution, and fiber transverse breakage. The rat model was also extended to lung retention of other

synthetic vitreous fibers, but extension of the human model to other synthetic vitreous fibers has not been reported (Yu et al. 1998a, 1998b). The dosimetric models for refractory ceramic fibers predict fiber lung concentration as a function of time for both humans and rodents for given air concentrations of fibers with specified distributions of length and diameter. The models can be used to convert exposure levels in animal inhalation toxicity and cancer studies to human equivalent exposure levels (Appendix A describes the use of these models in deriving a chronic inhalation MRL for refractory ceramic fibers). As discussed in Section 3.4.5, several quantitative human cancer risk estimates have been prepared using the data from the RCF1 2-year rat bioassay and the lung deposition and clearance models developed by C.P. Yu and colleagues (Maxim et al. 2003b; Moolgavkar et al. 1999, 2000; Turim and Brown 2003; Yu and Oberdörster 2000).

In contrast to the relatively robust understanding of fiber pharmacokinetics in animals and humans, understanding of the relative sensitivity of rodents and humans to synthetic vitreous fibers or asbestos fibers (i.e., the relative pharmacodynamics) is poor. For asbestos, rats appear to be a suitable *qualitative* model for humans given that effects observed in groups of workers exposed to high levels of airborne asbestos (chronic inflammation, pulmonary fibrosis, lung cancer, and mesothelioma) have also been observed in rat inhalation studies (Agency for Toxic Substances and Disease Registry 2001). However, similar *qualitative* comparisons between rodent and human responses to synthetic vitreous fibers are not possible. Available epidemiological studies of workers involved in the manufacture of fibrous glass, rock wool, or slag wool, or in the manufacture of refractory ceramic fibers have not found consistently increased risks for nonmalignant respiratory disease, lung cancer, or mesothelioma, although pulmonary fibrosis, lung cancer, and mesothelioma have been demonstrated in rats and hamsters exposed by inhalation to the most potent synthetic vitreous fibers (see Section 3.2).

For asbestos, limited *quantitative* data are insufficient to conclusively determine the relative sensitivity of humans and rodents to fibers, although several hypotheses have been proposed on this issue. Rodelsperger and Woitowitz (1995) proposed that humans may be more susceptible to asbestos's capability to induce mesothelioma based on a finding that lung fiber concentrations in a group of humans who died from asbestos-induced mesothelioma were markedly higher than concentrations in a bioassay of crocidolite-exposed rats. Earlier, Rowe and Springer (1986) proposed that humans and rodents may be equally sensitive to asbestos based on a comparison of estimated human lung cancer risks based on rodent inhalation bioassays and those derived in epidemiological studies of asbestos-exposed workers. Maxim and McConnell (2001) analyzed lung fiber concentrations associated with pulmonary fibrosis in rats and

hamsters exposed to a series of asbestos (crocidolite, chrysotile) and synthetic vitreous fibers (rockwool MMVF21 and refractory ceramic fiber RCF1) and compared these with fiber concentrations in autopsied lungs from several studies of workers with asbestosis (i.e., pulmonary fibrosis from asbestos exposure). Estimated concentrations in rodents ranged from $1.7x10^6$ to $20x10^6$ fibers (>20 μm long) per g dry lung compared with $1.6x10^6$ to $30x10^6$ fibers (>20 μm long) per g dry lung in humans. Maxim and McConnell (2001) concluded, based on these and other considerations, that "there seems little reason to believe that humans and rats have greatly different sensitivities with respect to the development of pulmonary fibrosis or lung cancer."

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that

are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding the possible effects of synthetic vitreous fibers on the neuroendocrine axis in humans or animals or in *in vitro* systems.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek

1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information was located specifically concerning health effects in children exposed to synthetic vitreous fibers. There was no indication from the available literature that specialized respiratory defense mechanisms might be less active or underdeveloped in children relative to adults. Results from animal studies indicate that inflammation, fibrosis, and cancer of the lung or pleura are possible outcomes resulting from repeated inhalation exposure to certain synthetic vitreous fibers depending on the exposure dose, exposure duration, fiber dimensions, and fiber durability. However, no studies were located that have compared immature and mature animals with respect to pharmacokinetics of, or susceptibility to, inorganic fibers of any type (including asbestos) by any route of exposure.

No human or animal studies were located regarding the possible developmental toxicities of synthetic vitreous fibers by any route of exposure. Direct effects on the developing fetus would be unexpected given the very small, if any, absorption of synthetic vitreous fibers by the lungs, gastrointestinal tract, or skin. For asbestos fibers of various types, no consistent indication of potential for developmental toxicity

was indicated in several oral administration studies with rats, mice, and hamsters (Agency for Toxic Substances and Disease Registry 2001).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to synthetic vitreous fibers are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by synthetic vitreous fibers are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible."

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Synthetic Vitreous Fibers

Uncoated or coated fibers in bronchoalveolar lavage fluid samples or in autopsied or surgically resected lung tissue samples are the principal biomarkers of exposure to biopersistent asbestos fibers (Agency for Toxic Substances and Disease Registry 2001).[1] However, similar biomarkers to identify or quantify human exposure to synthetic vitreous fibers, which are less biopersistent than asbestos fibers, have not been developed for routine clinical use. Nevertheless, aluminum-silicate fibers with chemical compositions consistent with synthetic vitreous fibers have been detected in human lung tissues (McDonald et al. 1990; Roggli 1989; Sébastien et al. 1994) and in bronchoalveolar lavage samples (Dumortier et al. 2001).

For example, among 1,800 bronchoalveolar samples submitted to a Belgium hospital between 1992 and 1997 for fiber analysis, pseudoasbestos bodies were detected in samples from nine patients (0.5%) (Dumortier et al. 2001). In samples from these nine patients (all of whom had occupational experience with furnaces or welding), fibers of composition consistent with refractory ceramic fiber composition were detected in 42% of core fibers analyzed (Dumortier et al. 2001). Other nonasbestos fibers and asbestos fibers accounted for 28 and 30% of the core fibers analyzed in these samples, respectively.

In another study, lung fiber concentrations were determined in autopsied tissue samples from a subset of deaths occurring between 1950 and 1979 in a cohort of U.S. workers involved in the manufacture of synthetic vitreous fibers (McDonald et al. 1990). The 145 autopsied tissue samples analyzed represented about 3% of the deaths that occurred in the cohort during this period. Lung fiber concentrations were

[1] Particles or fibers that are deposited in the lung and are too large to be phagocytized by alveolar macrophages may become coated with an iron-rich protein coat. The generic term for these structures is ferruginous bodies. When the core fiber is asbestos, the resultant structure is termed an asbestos body (Agency for Toxic Substances and Disease Registry 2001). Ferruginous bodies having the appearance of asbestos bodies under light microscopy and a nonasbestos core fiber have been termed pseudoasbestos bodies (Dumortier et al. 2001).

compared with concentrations in 124 autopsied referents who had no known occupational experience with synthetic vitreous fibers, were matched for location of death (i.e., hospital), age, and year of death, and died from causes other than malignant disease. Lung fiber concentrations (lengths >5 μm and length:diameter ratio >3:1) determined by phase contrast microscopy were about 60% higher in workers than referents. Electron microscopy (coupled with energy dispersive spectrometry and selected area electron diffraction) showed no statistically significant excess of any particular type of fiber in the workers compared with the referents, although asbestos fibers were detected with greater frequency than synthetic vitreous fibers in both workers and referents. Nonasbestos fibers described as "siliceous" displayed a strong energy dispersive signal for silicon without sodium, aluminum, potassium, calcium, titanium, or iron signals and represented >90% of fibers identified as synthetic vitreous fibers. However, lung samples from only 26% of the workers contained any synthetic vitreous fibers. The low detection frequency of synthetic vitreous fibers in the worker lung samples may reflect both low exposure concentrations and low biopersistence of these fibers.

In animal inhalation experiments with synthetic vitreous fibers, concentrations of fibers in the lung have been used to assay internal doses (e.g., Hesterberg et al. 1993c, 1999; Mast et al. 1995a, 1995b; McConnell et al. 1999). Based on rat experiments involving intraperitoneal injection of three different types of synthetic vitreous fibers, urinary levels of titanium or barium were proposed as potential biomarkers of exposure to synthetic vitreous fibers that contain these elements normally present in humans and animals in small quantities (Wastiaux et al. 1994). Reports of further development of urinary titatnium or barium as biomarkers of exposure to synthetic vitreous fibers were not located.

3.8.2 Biomarkers Used to Characterize Effects Caused by Synthetic Vitreous Fibers

Epidemiological studies of synthetic vitreous fiber manufacturing workers have not found consistent evidence for increased risks of malignant or nonmalignant respiratory or pleural effects, but results from animal experiments indicate that repeated inhalation exposure to synthetic vitreous fibers may result in pulmonary or pleural fibrosis, lung cancer, or mesothelioma, depending on fiber dimensions, fiber durability in the lung, duration of exposure, and exposure levels.

The chest x-ray is the most common means of detecting the onset of pleural or pulmonary changes that may precede or accompany fibrosis (i.e., irreversible scarring of lung or pleural tissue that can lead to restricted breathing). The International Labour Office (ILO) established a classification system for

profusion of opacities in chest x-rays that includes four categories of increasing severity, each with three subcategories: 0 (0/-, 0/0, 0/1); 1 (1/0, 1/1, 1/2); 2 (2/1, 2/2, 2/3); and 3 (3/2, 3/3, 3/4) (ILO 1980). The American Thoracic Society (1986) recommends that chest x-rays be scored for pleural and pulmonary changes separately because of the experience with asbestos-exposed workers indicating that pleural and pulmonary fibrosis have differences in "epidemiology, clinical features, and prognosis." Computerized tomography (CT) and high-resolution computed tomography provide alternative techniques to the chest x-ray that may more sensitively detect pleural and pulmonary changes in some cases (Agency for Toxic Substances and Disease Registry 2001). Lung function tests are also useful to characterize the development of pulmonary or pleural fibrosis; forced vital capacity is diminished with increasing severity of pulmonary or pleural fibrosis.

Clinical diagnostic criteria for pulmonary fibrosis include chest x-rays with small irregular opacifications of a profusion of 1/1 or greater, impaired forced vital capacity below the lower limit of normal, and a diffusing capacity below the lower limit of normal (American Thoracic Society 1986). Pleural changes associated with chronic inflammation from inhaled fibers or particles include pleural plaques, pleural fibrosis (also referred to as thickening or calcification), and pleural effusions. Pleural plaques are localized or diffuse areas of thickening of the pleura that appear as opaque, shiny, and rounded lesions in the chest x-ray. Pleural fibrosis represents a more pronounced thickening or scarring that, when severe, can make the pleura appear as a thick peel encasing the lung in chest x-rays. Persons with pleural fibrosis can experience chest pain and impaired pulmonary functions, but persons with pleural plaques alone usually do not (American Thoracic Society 1986). Pleural effusion is the exudation of cell-containing fluid from lung tissue into the pleural cavity, which is often taken as an early manifestation of exposure to asbestos fibers (American Thoracic Society 1986). Pleural effusions have been reported in groups of people exposed occupationally to asbestos (Agency for Toxic Substances and Disease Registry 2001), but have not been reported in workers involved in the manufacture of synthetic vitreous fibers.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Epidemiological and clinical studies of asbestos workers have indicated that workers who smoked tobacco had greater risks of developing lung cancer and pulmonary fibrosis than workers who did not smoke, and that smoking may increase these risks by more than risks predicted by an additive model (see Agency for Toxic Substance and Disease Registry 2001 for review). In contrast, the studies provided no indication that smoking increased the risk of mesothelioma. The mechanism of this interaction is not

fully understood, but there is evidence to suggest that smoking may decrease the ability of lungs to clear fibers or other particles. For example, the lungs of smoking workers with heavy asbestos occupational exposure showed higher concentrations of chrysotile and amosite fibers compared with nonsmoking workers (Churg and Stevens 1995), and the clearance rate of short chrysotile fibers was decreased by 30% in guinea pigs after coexposure to chrysotile and cigarette smoke compared with guinea pigs exposed to chrysotile alone (Churg et al. 1992).

A similar interaction between smoking and inhalation exposure to synthetic vitreous fibers in jointly affecting lung cancer or pulmonary fibrosis is plausible, but direct evidence to support the possible interaction is very limited. In a study of European refractory ceramic fiber production workers, a statistically significant association between indices of cumulative exposure to fibers and decreased pulmonary function was observed in workers who smoked, but not in nonsmokers (Cowie et al. 2001; Rossiter et al. 1994; Trethowan et al. 1995). Alveolar macrophages from rats exposed to sidestream cigarette smoke produced statistically significantly greater quantities of a cytokine involved in regulating cellular proliferation (tumor necrosis factor) in response to chrysotile fibers *in vitro* than did macrophages from rats not exposed to smoke (Morimoto et al. 1993). Refractory ceramic fibers also induced tumor necrosis factor production by macrophages *in vitro*. Macrophages from smoke exposed rats produced more tumor necrosis factor than macrophages from nonexposed rats, but the difference was not statistically significant (Morimoto et al. 1993). The only other published finding of relevance to the possible interactive effects smoking and exposure to synthetic vitreous fibers is the observation that *in vitro* oxidative damage to calf thymus DNA (assayed as the formation of 8-hydroxydeoxyguanosine residues) produced by cigarette smoke condensate and rockwool fibers together was greater than the sum of the damage by each agent alone (Leanderson and Tagesson 1989).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to synthetic vitreous fibers than will most persons exposed to the same level of synthetic vitreous fibers in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of synthetic vitreous fibers, or compromised function of organs affected by synthetic vitreous fibers. Populations who are at greater risk due to their unusually high exposure to synthetic vitreous fibers are discussed in Section 6.7, Populations With Potentially High Exposures.

Persons with impaired pulmonary clearance mechanisms (e.g., due to chronic exposure to cigarette smoke or repeated exposure to dusty air leading to high burdens of particles in the lung) or genetically determined relatively poor ability to detoxify reactive oxidative molecules produced during pulmonary disposition of fibers (e.g., reactive oxygen radicals or nitrogen oxide) may be more susceptible than others to possible nonmalignant or malignant pulmonary or pleural disorders from chronic exposure to synthetic vitreous fibers. Direct evidence in support of these hypotheses, however, is lacking for synthetic vitreous fibers, except for the observation that cumulative exposure indices were associated with decreased pulmonary function in European refractory ceramic fiber workers who smoked, but not in nonsmokers (Cowie et al. 2001; Rossiter et al. 1994; Trethowan et al. 1995).

In case-control studies of asbestos-exposed persons, associations have been observed between deletion of the gene (GSTM1) encoding one class of glutathione S-transferase (GSTμ), an enzyme that protects against oxidative tissue damage, and increased risks for mesothelioma, other cancers, or nonmalignant pulmonary disorders (Hirvonen 1997; Hirvonen et al. 1996; Kelsey et al. 1997). Increased risks for developing nonmalignant pulmonary disorders or mesothelioma were also observed among persons with histories of high-level asbestos exposure who lacked the GSTM1 gene and had a slow genotype for N-acetyltransferase 2 (NAT2), compared with risks in exposed subjects with the GSTM1 gene and the fast NAT2 genotype (Hirvonen et al. 1996). Slow acetylation by NAT2 may lead to accumulation of polyamines that stimulate cell proliferation.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to synthetic vitreous fibers. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to synthetic vitreous fibers. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to synthetic vitreous fibers:

Standard texts of medical toxicology (e.g., Ellenhorn et al. 1997; Goldfrank et al. 1998) do not provide specific information about treatment of acute irritation effects or possible chronic effects from exposure to synthetic vitreous fibers, but recommend minimizing exposure. Since the early 1990s, manufacturers of

synthetic vitreous fibers have been making modifications to new products in order to make them more biosoluble (i.e., less biopersistent) and potentially less hazardous than older products (Hesterberg and Hart 2001; IARC 2002).

3.11.1 Reducing Peak Absorption Following Exposure

Absorption of synthetic vitreous fibers is expected to be negligible following inhalation, ingestion, or dermal exposure. Recommendations have been made to avoid contact with the fibers by wearing protective clothing and using ocular and respiratory protection when working with materials containing synthetic vitreous fibers and to minimize physical disturbance of the material and generation of dusts, in order to avoid the acute dermal, respiratory, or ocular irritation experienced from contact with synthetic vitreous fibers (e.g., "fiberglass itch"), and prevent the possible pulmonary or pleural disorders from chronic inhalation exposure (Ellenhorn et al. 1997; Goldfrank et al. 1998; Jeffress 1999; Mentzer 1999; OSHA 1999). Rinsing of exposed areas with water also minimizes contact.

3.11.2 Reducing Body Burden

As discussed in Section 3.4, the principal pathways by which inhaled and deposited synthetic vitreous fibers are removed from the respiratory tract involve: (1) direct or macrophage-mediated mechanical mucociliary translocation to the pharynx, swallowing into the gastrointestinal tract, and elimination in the feces; (2) dissolution; and (3) transverse breakage of long fibers into shorter fibers. To date, there are no clinical methods to enhance or supplement these natural methods of elimination of inhaled fibers that deposit on the epithelial surfaces of the respiratory tract.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanisms by which repeated exposure to airborne synthetic vitreous fibers may cause pulmonary or pleural disorders are poorly understood (see Section 3.5), and there are no tested methods of interference. It is plausible that repeated exposure to the more durable synthetic vitreous fibers could also cause pulmonary or pleural disorders in humans as it has been observed to do in laboratory rodents.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of synthetic vitreous fibers is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of synthetic vitreous fibers.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

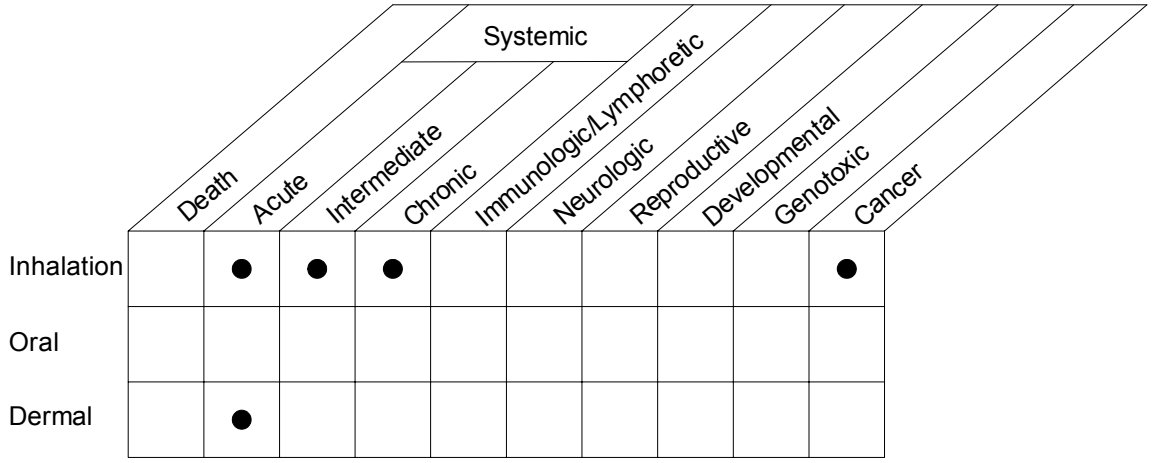
3.12.1 Existing Information on Health Effects of Synthetic Vitreous Fibers

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to synthetic vitreous fibers are summarized in Figure 3-2. The purpose of this figure is to illustrate the existing information concerning the health effects of synthetic vitreous fibers. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

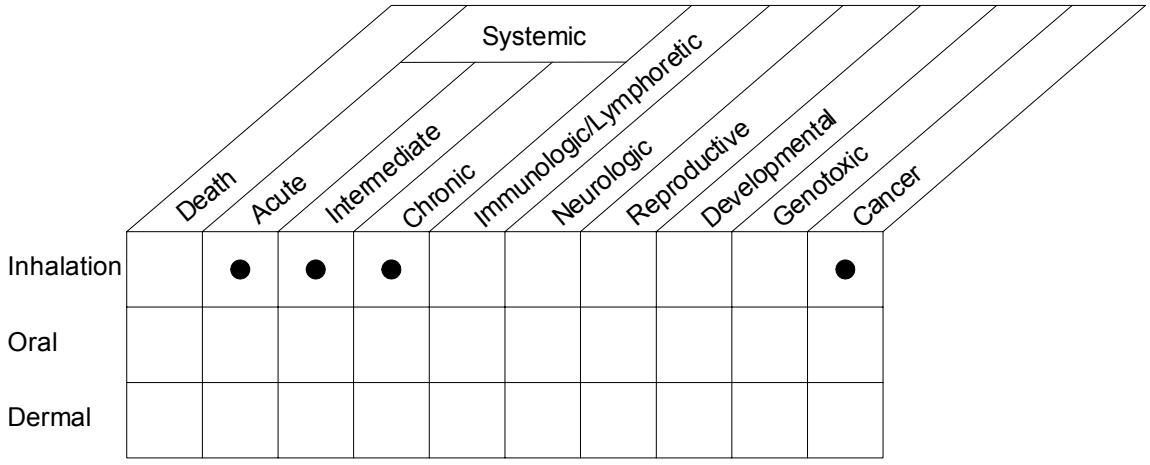
3.12.2 Identification of Data Needs

Acute-Duration Exposure. As discussed in Section 3.2, acute occupational exposure to synthetic vitreous fibers including fiberglass fabrics and insulation materials has been associated with reversible

Figure 3-2. Existing Information on Health Effects of Synthetic Vitreous Fibers



Human



Animal

● Existing Studies

symptoms of irritation of the upper respiratory tract (ACGIH 2001; Horvath 1995; Milby and Wolf 1969; Nasr et al. 1971; Newball and Brahim 1976; Petersen and Sabroe 1991; Thriene et al. 1996), the skin (Bendsoe et al. 1987; Bjornberg 1985; Bjornberg and Lowhagen 1977; Bjornberg et al. 1979a, 1979b, 1979c; Eun et al. 1991 Fisher 1982; Fisher and Warkentin 1969; Heisel and Hunt 1968; Kiec-Swierczynska and Szymczk 1995; Koh and Khoo, 1995; Longley and Jones 1966; Peterson and Sabroe 1991; Possick et al. 1970; Stam-Westerveld et al. 1994; Tarvainen et al. 1993; Thriene et al. 1996), and the eyes (Longley and Jones 1966; Petersen and Sabroe 1991; Stokholm et al. 1982). The skin irritation has been associated with fibers of diameter >5 μm and often becomes less pronounced with continued exposure (ACGIH 2001; Heisel and Hunt 1968; Stam Westerveld et al. 1994).

The available human data adequately identify reversible skin irritation as a concern from acute dermal exposure. The data support occupational health and public health recommendations to limit dermal contact and airborne exposure by limiting the generation of dusts from materials containing synthetic vitreous fibers and by wearing loose protective clothing, gloves, and ocular and respiratory protection when handling the material.

Acute inhalation studies in animals are limited to rodent studies with RCF1 that observed pulmonary and pleural inflammation (Everitt et al. 1994; Gelzleichter et al. 1996a, 1996c). Other studies have observed nonneoplastic and neoplastic health effects caused by injection or implantation (e.g., single acute dosing) of synthetic vitreous fibers into the intraperitioneal or intrapleural cavities of animals (Adachi et al. 1991; Davis et al. 1984; Feron et al. 1985; Mohr et al. 1984; Pickrell et al. 1983; Pigott and Ishmael 1981; Pott et al. 1987; Renne et al. 1985; Smith et al. 1987; Stanton and Wrench 1972; Stanton et al. 1977; Wright and Kuschner, 1977). Their relevance to human inhalation exposure is unclear because of the high doses and rapid dose rates used, the bypassing of the natural defense systems of the nasal and upper respiratory system, and the overloading or lack (for intraperitoneal studies) of pulmonary clearance mechanisms. No acute inhalation MRL was derived because data describing dose-response relationships for irritation of the upper respiratory tract in humans or animals are not available.

No acute-duration oral exposure studies in humans or animals were identified. The oral route of exposure is not of public health concern for synthetic vitreous fibers; therefore, no data need is identified.

Intermediate-Duration Exposure. Epidemiologic studies involving inhalation exposure have tended to exclude persons with intermediate-duration (<1 year) exposure, due to associated confounding

factors. In animals, multiple exposure-level experiments were conducted for RCF1, the glass wools MMVF10 and MMVF11, the rock wool MMVF21, and the slag wool MMVF22 (Hesterberg et al. 1999; Mast et al. 1995b; McConnell et al. 1994), but other fiber types were tested only at single (usually high) concentrations. The studies were designed as chronic studies, but include interim sacrifice data describing dose-response relationships for effects from intermediate-duration inhalation exposure.

Virtually all of the fibers tested caused reversible pulmonary inflammation, including the refractory ceramic fibers RCF1, RCF2, RCF3, and RCF4, the insulation glass wools MMVF10 and MMVF11, the rock wool MMVF21, the slag wool MMVF22, the durable glass fiber MMVF33, the high-temperature rock wool MMVF 34, the high-silica synthetic vitreous fiber X607, the special-purpose 104E-glass fiber, GB100R glass wool, and C102/C104 blend fibrous glass (Cullen et al. 2000; Goldstein et al. 1983; Haratake et al. 1995; Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999). Only one study reported a NOAEL, for Code 104 glass wool (Muhle et al. 1987).

Interstitial or pleural fibrosis was seen in rodents exposed to the refractory ceramic fibers RCF1, RCF2, RCF3, and RCF4, the durable glass fiber MMVF33, and the special purpose 104E-glass following intermediate-duration exposure (Cullen et al. 2000; Mast et al. 1995a, 1995b; McConnell et al. 1999), but no increase in fibrosis was seen in animals exposed to MMVF10, MMVF11, MMVF34, or X607 (Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; McConnell et al. 1999).

The available animal data adequately identify pulmonary or pleural effects as potential health hazards from intermediate-duration inhalation exposure to synthetic vitreous fibers. The data also provide adequate descriptions of dose-response relationships for these effects in rats from samples of glass wools, rock wool, slag wool, and refractory ceramic fibers.

A chronic inhalation MRL was derived for the refractory ceramic fiber, RCF1, based on pulmonary inflammation in rats as the critical effect (see Section 2.3 and Appendix A). The MRL derivation used rat and human lung deposition and clearance models to extrapolate rat exposure levels to human equivalent concentrations and was based on the assumption that the responses in rats would occur in humans at the same dose of fibers deposited in the alveolar region of the lung. The interim sacrifice data from the chronic study indicated that dose-response relationships for this effect were similar for chronic and intermediate durations. Although an intermediate inhalation MRL for refractory ceramic fibers was not

derived, the data indicate that it would be similar to the chronic MRL. It is expected that the chronic MRL can be used reliably to assess effects from intermediate-duration exposures. Additional data for intermediate-duration exposure to RCF1 do not appear to be needed.

Adequate rat data are also available for intermediate and chronic inhalation exposure to MMVF10, MMVF11, MMVF21, and MMVF22. However, no intermediate or chronic inhalation MRLs were derived because of the uncertainty in extrapolating from rats to humans in the absence of human lung deposition and clearance models for these synthetic vitreous fibers. However, when such models are available, the rat studies will provide adequate data for deriving intermediate and chronic inhalation MRLs for glass wool, rock wool, and slag wool.

No intermediate-duration oral or dermal exposure studies in humans or animals were identified. Repeated exposure by the oral route is of relatively low concern for the general population; therefore, no data need has been identified at this time. For dermal exposure, the available data demonstrating acute reversible skin irritation from direct contact with insulation materials containing synthetic vitreous is adequate to support public health recommendations to wear gloves and protective clothing (and other protective devices including eye and respiratory protection) when handling materials containing synthetic vitreous fibers. No data need has been identified for potential health effects from intermediate-duration dermal exposure.

Chronic-Duration Exposure and Cancer. The most biologically significant effect found in retrospective and longitudinal evaluations of the health of workers involved in the manufacture of refractory ceramic fibers in the United States (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002) and Europe (Cowie et al. 2001; Trethowan et al. 1995) is a low prevalence of pleural plaques (about 3%). However, consistent statistically significant associations with exposure to refractory ceramic fibers were only found in the U.S. cohort (Lentz et al. 2003; Lockey et al. 1996, 2002). Consistent exposure-related effects on pulmonary function have not been found in these cohorts (Burge et al. 1995; Cowie et al. 2001; Lockey et al. 1998).

Adverse findings in cross-sectional health evaluation studies of workers involved in the manufacture of continuous glass fibers, glass wool, or rock and slag wool are restricted to elevated prevalences of self-reported respiratory symptoms (e.g., coughing, bronchitis) (Albin et al. 1998; Clausen et al. 1993; Engholm and von Schmalensee 1982; Kilburn et al. 1992); evidence for elevated prevalences of pleural

plaques in these workers is inadequate (Hughes et al. 1993; Kilburn and Warshaw 1991; Kilburn et al. 1992; Sanden and Jarvholm 1986; Scansetti et al. 1993; Weill et al. 1983).

Cohort mortality and case-control studies have tracked nonneoplastic and neoplastic causes of mortality among groups of workers involved in the manufacture of fibrous glass, rock wool, or slag wool without finding conclusive evidence of increased risks associated with exposure (Bayliss et al. 1976; Bertazzi et al. 1986; Boffetta et al. 1999; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Kjaerheim et al. 2001; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Sali et al. 1999; Saracci et al. 1984; Shannon et al. 1984, 1987, 1990; Simonato et al. 1986a, 1987; Watkins et al. 1997). Similar cohort mortality or case-control studies of workers involved in the manufacture of refractory ceramic fibers are restricted to a mortality study of male workers employed at two U.S. manufacturing plants (LeMasters et al. 2003). In an initial report of the mortality experience of this cohort (about 90% of which is still alive), the only statistically significant excess mortality was for deaths associated with cancer of the urinary system. No mesotheliomas and no excess deaths associated with respiratory cancers or nonmalignant respiratory disease were found. The excess urinary cancer deaths may be a chance finding given the wide confidence interval for the SMR, the large number of statistical tests (n=46) that were conducted, and the lack of a plausible mechanistic explanation of how fibers may increase the risk for urinary cancer mortality. Continued monitoring of the mortality experience of this cohort is planned.

In animals, chronic-duration inhalation studies were primarily continuations of intermediate-duration studies, with pulmonary inflammation observed for all fibers tested and fibrosis observed for the refractory ceramic fibers and MMVF 33 (see Section 3.2). The special-purpose 104E-glass was not tested in a chronic-duration study. Although C102/C104 blend fibrous glass was not fibrogenic at 8 months, pulmonary fibrosis was observed by 18 months (Goldstein et al. 1983). Pleural mesotheliomas were observed in rodents exposed to refractory ceramic fibers (RCF1, RCF2, and RCF3), MMVF33, and 104E-glass (Cullen et al. 2000; Mast et al. 1995a; McConnell et al. 1999; Smith et al. 1987). Lung tumor incidence (adenomas, carcinomas, or the combined incidence) were elevated in rodents exposed to RCF1, RCF2, RCF3, RCF4, or 104E-glass (Cullen et al. 2000; Mast et al. 1995a, 1995b; McConnell et al. 1995), but not in studies with other synthetic vitreous fibers including MMVF10, MMVF11, MMVF 21, MMVF22, MMVF34, Code 104 glass wool, GB100R glass wool, high-silica synthetic vitreous fiber X607, or special-purpose 100/475 glass microfiber (Cullen et al. 2000; Goldstein et al. 1983; Haratake et

al. 1995; Hesterberg et al. 1993c, 1998b; Kamstrup et al. 2001; Mast et al. 1995a, 1995b; McConnell et al. 1994, 1999; Muhle et al. 1987).

As discussed in the previous section, a chronic inhalation MRL was derived for the refractory ceramic fiber, RCF1, based on pulmonary inflammation in rats as the critical effect (see Section 2.3 and Appendix A). One area of uncertainty associated with the critical study for the chronic MRL is the degree to which the dose-response relationship for pulmonary inflammation is affected by the nonfibrous particles in the aerosols to which the rats were exposed. Nonfibrous particles (with aspect ratios <3:1) have been reported to account for about 25% of the mass in RCF1 aerosols (Bellmann et al. 2001). Results from 3-week exposure studies with rats suggest that pulmonary responses to RCF1a, a material with only 2% of its mass accounted for by nonfibrous particles, are less severe than those induced by RCF1 at similar exposure levels (Bellmann et al. 2001). Additional research may be useful to quantitatively determine the effect of nonfibrous particles on the dose-response relationship for pulmonary inflammation from chronic exposure to refractory ceramic fibers.

Adequate rat data are also available for intermediate and chronic inhalation exposure to the glass wools, MMVF10 and MMVF11, a rock wool, MMVF21, and a slag wool, MMVF22. However, no intermediate or chronic inhalation MRLs were derived because of the uncertainty in extrapolating from rats to humans in the absence of human lung deposition and clearance models for these synthetic vitreous fibers. When such models are available, the rat studies will provide adequate data for deriving intermediate and chronic inhalation MRLs for glass wool, rock wool, and slag wool.

Workers involved in the installation or removal of insulation materials with synthetic vitreous fibers are expected to be exposed to higher airborne levels of fibers than manufacturing workers, but research that monitored health status and mortality patterns in groups of these types of workers is limited. Additional longitudinal monitoring of the respiratory health of insulation workers (and their exposure conditions) may be helpful in a better assessment of the health safety of their work environment.

No chronic-duration oral or dermal exposure studies in humans or animals were identified, although experimental studies with human subjects, case reports, and occupational exposure experience document the well-known acute, but reversible, skin irritation caused by direct dermal contact with insulation glass wools. Repeated exposure by these routes is not of high concern for the general public; therefore, no data needs for these routes have been identified at this time. Reinforcing the lack of concern for health effects

by oral exposure to fibrous materials, results from several studies of rats exposed for life to several types of asbestos found no convincing evidenc for nonmalignant disease in the exposed rats (Agency for Toxic Substances and Disease Registry 2001).

Genotoxicity. No evidence for genotoxic activity of several synthetic vitreous fibers was found in bacterial mutation assays (Chamberlain and Tarmy 1977) or sister chromatid exchange assays in cultured human cells (Casey 1983). However, cytogenetic effects induced by synthetic vitreous fibers in mammalian cells *in vitro* include chromosomal aberrations (Brown et al. 1979a, 1979b); morphological transformations (Gao et al. 1995; Hesterberg and Barrett 1984; Hesterberg et al. 1985; Oshimura et al. 1984; Whong et al. 1999); micronuclei and multinuclei (Dopp and Schiffmann 1998; Dopp et al. 1997; Hart et al. 1992; Ong et al. 1997; Peraud and Riebe-Imre 1994; Zhong et al. 1997); polyploidy (Koshi et al. 1991; Sincock et al. 1982); and DNA strand breaks and DNA-DNA interstrand crosslinks (Wang et al. 1999b). In addition, several synthetic vitreous fiber types have been demonstrated to damage isolated DNA (Donaldson et al. 1995c) and to hydroxylate 2-deoxyguanosine to 8-hydroxydeoxyguanosine, presumably via hydroxyl radicals (Leanderson et al. 1988, 1989).

There is evidence that fiber dimensions can influence *in vitro* cytogenetic activities (Hesterberg and Barrett 1984; Hesterberg et al. 1985; Ong et al. 1997) and that synthetic vitreous fibers are often less genotoxically active than asbestos fibers (e.g., Donaldson et al. 1995c; Janssen et al. 1994a; Leanderson et al. 1988, 1989; Peraud and Rieve-Imre 1994; Wang et al. 1999b). For example, thin glass fibers (diameters 0.1–0.2 μm, lengths >10 μm) were very active in transforming Syrian hamster embryo cells, whereas thick glass fibers (diameter about 0.8 μm) were much less potent (Hesterberg and Barrett 1984). Milling of the thin glass fibers to reduce the length to <1 μm diminished the transforming activity.

The available evidence is sufficient to suggest that synthetic vitreous fibers may produce cytogenetic changes in *in vitro* systems, but data regarding *in vivo* genotoxicity is lacking. *In vivo* data may be helpful to further assess the genotoxic potential of synthetic vitreous fibers.

Reproductive Toxicity. There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce reproductive effects. Given the limited degree to which synthetic vitreous fibers are absorbed into the body, there is no mechanistic basis to suspect that reproductive effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

Developmental Toxicity. There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce developmentally toxic effects. As with reproductive toxicity, there is no empirical or mechanistic basis to suspect that developmental effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

Immunotoxicity. There are no studies in humans or animals specifically designed to examine the potential for synthetic vitreous fibers to affect the immunological or lymphoreticular systems following inhalation, oral, or dermal exposures. There are several reports of immune system depression in asbestos-exposed workers who developed asbestosis or cancer (see Agency for Toxic Substance and Disease Registry 2001), but whether or not the depression was directly caused by asbestos or by the diseased state is unknown. Given the lack of increased reporting of symptoms of allergy or immune system depression in health surveillance studies of workers involved in the manufacture of refractory ceramic fibers or insulation wools (Clausen et al. 1993; Cowie et al. 2001; Ernst et al. 1987; Gross 1976; Hansen et al. 1999; Hill et al. 1973; Hughes et al. 1993; Kilburn et al. 1992; LeMasters et al. 1998; Lockey et al. 1998; Moulin et al. 1988; Nasr et al. 1971; Sanden and Jarvholm 1986; Trethowan et al. 1995; Weill et al. 1983; Wright 1968), immunological effects do not appear to be a critical public health concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

Neurotoxicity. There are no studies in humans or animals on the potential for synthetic vitreous fibers to produce neurotoxic effects. As with reproductive and developmental toxicity, there is no empirical or mechanistic basis to suspect that neurotoxic effects may be of concern from exposure to synthetic vitreous fibers. No data needs have been identified at this time.

Epidemiological and Human Dosimetry Studies. Studies of workers predominately involved in the manufacture of fibrous glass materials have focused on the prevalence of respiratory symptoms through the administration of questionnaires, pulmonary function testing, and chest x-ray examinations (Clausen et al. 1993; Gross 1976; Hill et al. 1973; Hughes et al. 1993; Nasr et al. 1971; Weill et al. 1983; Wright 1968). In general, these studies reported no consistent evidence for increased prevalence of adverse respiratory symptoms, abnormal pulmonary functions, or chest x-ray abnormalities; however, one study reported altered pulmonary function (decreased forced expiratory volume in 1 second) in a group of Danish insulation workers compared with a group of bus drivers (Clausen et al. 1993). Longitudinal health evaluations of workers involved in the manufacture of refractory ceramic fibers, fibrous glass, rock wool, or slag wool have not found consistent evidence of exposure-related changes in chest x-rays or

pulmonary functions, with the exception that pleural plaques were found in about 3% of examined U.S. refractory ceramic fiber manufacturing workers and that pleural plaque prevalence showed statistically significant trends with increasing exposure categories (LeMasters et al. 1994; Lentz et al. 2003; Lockey et al. 1996, 2002).

Epidemiologic studies (cohort mortality and case-control studies) of causes of mortality among groups of workers involved in the manufacture of fibrous glass, rock wool, or slag wool provide no consistent evidence for increased risks of mortality from nonmalignant respiratory disease, lung cancer, or pleural mesothelioma (Bayliss et al. 1976; Bertazzi et al. 1986; Boffetta et al. 1999; Buchanich et al. 2001; Chiazze et al. 1992, 1993, 1995, 1997, 2002; Enterline and Henderson 1975; Kjaerheim et al. 2002; Marsh et al. 1990, 2001a, 2001b, 2001c; Morgan 1981; Sali et al. 1999; Saracci et al. 1984; Shannon et al. 1984, 1987, 1990; Simonato et al. 1986a, 1987; Watkins et al. 1997). In an initial report of the only available cohort mortality study of refractory ceramic fiber workers, the only statistically significant excess mortality was for deaths associated with cancer of the urinary system (LeMasters et al. 2003). No mesotheliomas and no excess deaths associated with respiratory cancers or nonmalignant respiratory disease were found. Continued monitoring of the mortality experience of this cohort is planned.

As discussed in the "Chronic-Duration Exposure and Cancer" section, workers involved in the installation or removal of insulation materials with synthetic vitreous fibers are expected to be exposed to higher airborne levels of fibers than manufacturing workers, but monitoring of the health status and mortality patterns in groups of these types of workers is limited. Additional longitudinal monitoring of the respiratory health of groups of insulation workers (and their exposure conditions) may be helpful in a better assessment of the health safety of their work environment.

Biomarkers of Exposure and Effect.

Exposure. The most pertinent parameter for measuring exposure to synthetic vitreous fibers would be retained or deposited dose of fibers in the lung, a biomarker that is invasive and impossible to determine without autopsy or resection. The detection and chemical identification of fibers in bronchoalveolar lavage or sputum samples has been proposed as less invasive biomarkers of exposure to asbestos (Agency for Toxic Substances and Disease Registry 2001) and synthetic vitreous fibers (Dumortier et al. 2001), but these methods have not been fully developed as quantitative biomarkers of exposure. Further

development of noninvasive biomarkers of exposure may be useful to monitor workers exposed to dusty working conditions when installing or removing materials containing synthetic vitreous fibers.

Effect. No specific and sensitive biomarkers of disease induced by synthetic vitreous fibers are known. The chest x-ray represents the most widely used method to detect nonneoplastic and neoplastic lesions in the lung or pleura that may occur (as indicated by animal experiments) after long-term exposure to synthetic vitreous fibers (American Thoracic Society 1986). However, the chest x-ray would detect changes only after significant injury has occurred and would not indicate directly whether or not the changes were caused by synthetic vitreous fibers or some other lung toxicant such as cigarette smoke or asbestos. Computerized tomography has shown some promise for detecting early asbestos-related effects such as pleural plaques or thickening (Agency for Toxic Substances and Disease Registry 2001), and may be useful to monitor the health of workers repeatedly exposed to high levels of airborne synthetic vitreous fibers. Tests of lung function also detect relatively early signs of effects from lung toxicants, but provide only limited information regarding the possible cause. Given the evidence that pulmonary or pleural effects are not expected at airborne concentrations below current recommendations for occupational exposure limits (1 fiber/cc for insulation wools and 0.2 fiber/cc for refractory ceramic fibers; ACGIH 2001), current methods to monitor possible effects from synthetic vitreous fibers appear adequate, albeit lacking in specificity (i.e., chest x-ray, lung function tests, and computerized tomography). No data needs have been identified at this time.

Absorption, Distribution, Metabolism, and Excretion. As discussed in Section 3.4, rates of absorption of synthetic vitreous fibers across the epithelial layers of the respiratory tract, the gastrointestinal tract, and the skin are expected to be negligible given the relatively large physical dimensions of these elongated particles. The toxicokinetic variables of greatest relevance to the exposure route of greatest public health concern (inhalation) are: the extent and location of fiber deposition in the respiratory tract; the rates of deposited fiber removal by mucociliary transport, macrophage-mediated engulfment and clearance, and dissolution in lung fluid; and the translocation of fibers within and across the lung. These variables are of toxicological interest because fibers can accumulate in the lung leading to chronic and persistent pulmonary inflammation and, for the more durable synthetic vitreous fibers, tissue damage when rates of fiber deposition exceed rates of removal. For a variety of synthetic vitreous fibers and some amphibole fibers (which do not undergo dissolution in lung fluid), correlations have been demonstrated between the ability to induce pulmonary or pleural inflammation or tissue damage and several of these variables, including dissolution rates in synthetic lung fluid, fiber breakage rates, and

fiber lung clearance half-times (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a).

For several types of synthetic vitreous fibers, these processes have been well studied in animals, but not directly in human subjects. The animal study results provide enough information to support the development of models that predict lung deposition and retention of inhaled refractory ceramic fibers and other synthetic vitreous fibers (glass wools and rock wools) in rats (Yu et al. 1994, 1995b, 1996, 1998a, 1998b). Good agreement has been observed between model predictions and observed concentrations of fibers in the lungs of rats exposed to aerosols of refractory ceramic fibers or insulation wools for intermediate or chronic durations. Models to predict the deposition and retention of inhaled refractory ceramic fibers in humans have been developed based on known anatomical and physiological differences between rats and humans (Yu et al. 1995a, 1997). In the only testing of the human model, it was used to predict exposure concentrations from autopsied lung concentration data for three refractory ceramic fiber manufacturing workers (Yu et al. 1997). The predicted exposure concentrations were within the range of air concentrations measured for some manufacturing plants.

Models for lung retention and clearance of other synthetic vitreous fibers have not been developed. Development of human models for insulation wools will decrease uncertainty in extrapolating from chronic inhalation data for pulmonary inflammation in rats and facilitate the derivation of intermediate- and chronic-duration inhalation MRLs for these materials. Additional research to compare predictions from the human models with lung concentration data for human subjects with known exposures may help to decrease uncertainty in the validity of the model predictions.

The lung deposition and retention models incorporate information from the animal studies that the fraction of inhaled synthetic vitreous fibers deposited on the epithelial surfaces of the respiratory tract and the region where deposition occurs are determined by fiber dimensions, fiber mass density, ventilation parameters, and the structure and airway size of the respiratory tract (Dai and Yu 1998; Lippmann 1990; Morgan 1995; Yu et al. 1995a). Fibers with aerodynamic diameters >3–5 μm are predominately deposited in the upper airways and do not travel to the lower lung where gas exchange occurs. Fibers deposited in the upper airways are quickly removed by mucociliary transport to the pharynx and swallowing. The models also incorporate information from animal studies illustrating the following features of clearance of synthetic vitreous fibers from the lower lung: (1) fibers are cleared from the lower gas exchange region by macrophage engulfment and transport; (2) fibers longer than the diameter

of macrophages are poorly engulfed and cleared (i.e., shorter fibers are more rapidly cleared than longer fibers); (3) macrophage-mediated clearance is dependent on lung burden of particles (the rate of clearance slows at high lung burdens); (4) dissolution of synthetic vitreous fibers occurs in lung fluid (the dissolution rate varies with fibers of varying chemical composition); and (5) partially dissolved fibers more readily break into shorter fibers. The models do not describe translocation of deposited fibers from the lower lung into pleural tissue or the lymphatic system, although there is evidence from animal studies that small numbers of short and thin fibers are rapidly translocated to pleural tissues (Everitt et al. 1997; Gelzleichter et al. 1996a, 1999) and that translocation to lymph nodes can be considerable only under conditions that overload macrophage-mediated clearance mechanisms (Lee et al. 1981a; Morgan et al. 1982). Additional research on the extent and rate of translocation of fibers into pleural tissue, and conditions governing this process, may be useful in providing more a specific description of the target organ dose-response relationship for pleural effects (pleural fibrosis and mesothelioma) observed in rats exposed to the most durable of synthetic vitreous fibers, refractory ceramic fibers.

There are no toxicokinetic studies in humans or animals following oral or dermal exposure. Absorption and retention in the gastrointestinal tract and the skin are expected to be negligible. No data needs are identified at this time for toxicokinetic data for these routes of exposure.

Comparative Toxicokinetics. As discussed in Sections 3.4 and 3.5.3, differences in respiratory tract size and geometry, ventilation rates and patterns, and macrophage size between animal species and humans are expected to influence the retention of synthetic vitreous fibers in the lung. Lung deposition and clearance models that incorporate many of these interspecies differences have been developed for refractory ceramic fibers in rats, hamsters, and humans (Dai and Yu 1998; Yu et al. 1994, 1995a, 1995b, 1996, 1997). The models assume that dissolution rates, as well as transverse breakage rates and patterns (i.e., breakage of long fibers into shorter ones), are the same in animals and humans. The models predict that for refractory ceramic fiber size ranges and concentrations encountered in workplaces, (1) mouth-breathing leads to higher fractional deposition of inhaled fibers than nose-breathing in humans; (2) fractional deposition of inhaled fibers is less in rats and hamsters than in nose-breathing humans; (3) humans have 1–2.5 times less deposited fiber per unit alveolar surface area than rats and hamster; and (4) size dimensions (length and width) of fibers deposited in human lungs are larger than those of fibers deposited in lungs of rats and hamsters (Yu et al. 1995a).

The rat model has been extended to other synthetic vitreous fibers (i.e., several types of insulation wools), but, to date, the human model has not. As discussed in the previous section, development of human models for insulation wools will decrease uncertainty in extrapolating from chronic inhalation data for pulmonary inflammation in rats and facilitate in the derivation of intermediate- and chronic-duration inhalation MRLs for these materials.

There are no comparative toxicokinetic studies in humans or animals following oral or dermal exposure. Absorption and retention in the gastrointestinal tract and the skin are expected to be negligible in animals and humans. No data needs are identified at this time for comparative toxicokinetic data for these routes of exposure.

Methods for Reducing Toxic Effects. Information specific to synthetic vitreous fibers regarding treatment of acute irritation effects or possible chronic effects from exposure or reduction of body burdens have not been identified, although minimizing exposure, wearing protective clothing, and rinsing of exposed areas (e.g., skin and eyes) with water are recommended (Ellenhorn et al. 1997; Goldfrank et al. 1998; Jeffress 1999; Mentzer 1999; OSHA 1999).

As discussed in Section 3.5.1, the dose of fibers retained in the lower lung is a key determinant of the potential for fibers to induce toxic effects such as pulmonary inflammation, pulmonary fibrosis, lung cancer, or mesothelioma. Lung retention of fibers is the net result of lung deposition and clearance mechanisms including direct mucociliary clearance, macrophage-mediated clearance, dissolution rates, and transverse breakage of long fibers into shorter fibers. Once fibers are inhaled and deposited in the lung, there are no known treatment options to enhance the natural clearance mechanisms and reduce body burden after exposure. Additional research on physiological and molecular details of clearance mechanisms and mechanisms governing translocation into pleural tissue may provide clues for developing treatments to enhance clearance of the more biopersistent synthetic vitreous fibers from the lower lung and pleural tissue.

Observed correlations between toxic potencies and dissolution rates for various types of vitreous and mineral fibers indicate that the dissolution of fibers in lung fluid is a key determinant of potential toxicity that is influenced by chemical composition and structure and manufacturing processes (Bernstein et al. 2001a, 2001b; Eastes and Hadley 1996; Eastes et al. 2000; Hesterberg et al. 1998a; Hesterberg and Hart 2001; Wardenbach et al. 2000). Ongoing research to develop new synthetic vitreous fibers that are less

biopersistent holds promise as a method to avert or decrease the potential for producing toxic effects. For example, vitreous fibers with relatively high alumina and silica contents have been shown to favor a relatively uniform, slower rate of dissolution, but increasing content of oxides of calcium, magnesium, and potassium can lead to nonuniform rates of dissolution, faster breakage, and faster clearance (Eastes et al. 2000; Hesterberg and Hart 2001; Morgan 1994b; Potter and Mattson 1991).

As briefly discussed in Section 3.5.2, cellular and molecular events involved in fiber-induced nonneoplastic and neoplastic effect are poorly understood, but mechanistic studies (predominately with asbestos fibers) indicate that fibers retained in lung or pleural tissue may lead to cytotoxic and cytoproliferative changes as a result of increased production of reactive oxygen species that can damage cellular macromolecules, lead to cytotoxicity, and stimulate the release of inflammatory mediators, cytokines, and growth hormones (Churg et al. 2000; Driscoll 1996; IARC Expert Panel 1996). Several other mechanisms also have been proposed. Additional research on mechanisms of fiber-induced toxicity may eventually lead to the development of therapeutic approaches for reducing toxic effects from the biopersistent synthetic vitreous fibers or more efficient screening methods to evaluate the potential toxicities of newly developed synthetic vitreous fibers.

Children's Susceptibility. No information was located specifically concerning health effects in children exposed to synthetic vitreous fibers, and no studies were located that have compared immature and mature animals with respect to pharmacokinetics of, or susceptibility to, inorganic fibers of any type (including asbestos) by any route of exposure. There is no indication from the available literature that the pulmonary clearance mechanism might be less active or underdeveloped in children relative to adults. Direct effects on the developing fetus are not expected given the low absorption of synthetic vitreous fibers by the lung, gastrointestinal tract, and skin. Thus, there does not appear to be a need to conduct developmental toxicity tests for synthetic vitreous fibers. Additional research comparing pulmonary and pleural responses of immature and mature animals to the more biopersistent synthetic vitreous fibers may provide relevant information regarding the relative susceptibility of adults and children to the potential toxicity of synthetic vitreous fibers. Such experiments may be difficult to perform with immature animals, however, given the stress experienced by animals when they are fitted with nose-only inhalation apparatus (McConnell 1999).

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies funded solely by the U.S. government have not been identified. Other organizations have funded several large ongoing epidemiological studies of synthetic vitreous fiber manufacturing workers and the recent extensive animal toxicology studies reported in the published literature (see Section 3.2).